A systematic review of the factors affecting sperm binding and release from the oviduct using in vitro experimental animal models

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Running Title: Factors affecting Sperm release and Binding from the Oviductal epithelial cells in vitro

Summary Sentence: Herein we review factors that affect sperm binding and release from the oviductal epithelial cells in-vitro that has a direct effect on the fertilizing potential of sperm

Abstract

Background: After insemination, spermatozoa bind to epithelial cells of the isthmic part of the oviduct to form a functional sperm reservoir responsible for regulating sperm viability and capacitation prior to the ovulation signal that triggers its release. Understanding this information is essential for improving outcomes of in-vitro fertilization programs and semen-sorting process. **Objective:** This review aims to provide a comprehensive systematic assessment of the literature on the non-steroid hormone factors involved in sperm binding and release from the sperm reservoir in animal species in in-vitro experiments. **Methods:** PubMed, Web of Science, and Google Scholar databases were searched, and

eligible studies included articles published between 1st January 1990 and 31st July 2024 reporting molecules involved in sperm binding and release from the oviduct, as well as the impact of released sperm on in-vitro fertilization. **Results:** Sperm and oviducts from bovine, porcine, canine, camelid, equine, hamster and ovine were used and different culture systems such as epithelial explants, monolayers, and ex-vivo oviducts were established. The behaviour of sperm in the oviductal epithelium was influenced by several factors such as carbohydrates and their derivatives, seminal plasma proteins, glycoproteins, tyrosine phosphorylation of sperm, endocannabinoids, sex-sorting and glycosaminoglycans. Further, the seminal plasma proteins increased the binding ability of epididymal sperm to the oviductal explants. **Conclusions:** Future studies should focus on designing comparative research across various species. This may aid in identifying species-specific adaptations and conserved mechanisms in sperm-oviduct interactions, which may be helpful for conservation and breeding efforts.

Keywords: sperm binding, sperm release, oviductal epithelium, sperm, semen-sorting, *in-vitro* fertilization

1.0 Introduction

During copulation, significantly large numbers of sperm are ejaculated into the female genital tract. These numbers may reach 40 million and as much as 37.5 billion in humans and boar, respectively [1] .However, only a few reach the site of fertilization located in the ampulla region of the oviduct [1]. In most domestic animal species such as the cow and gilt, a proportion of sperms are stored and can survive in the female reproductive tract for at least 24 to 30 hours after insemination [2]. This feature is attributed to their ability to form intimate

interactions with the oviductal epithelial cells (OECs) to create sperm reservoir located mainly in the isthmus region of the oviduct [3].

It is now well known that sperm-oviduct interactions play critical roles in successful animal fertilization. Notably, these interactions help to reduce the chances of polyspermy, maintain sperms' oocyte-fertilizing competency as well as regulate capacitation and hyperactivation [3]. Evidence shows that sperms that fail to bind to the oviductal epithelium probably due to damage or altered morphology eventually become immotile and are unable to be released from the reservoir to fertilize the oocyte [4]. This feature suggests that sperm-oviductal interaction is also important for prolonging sperm survival and sperm selection to ensure that only competent spermatozoa have a chance to fertilize the oocyte [5].

Several factors influence sperm binding to and release from the OECs [1,2]. It has been determined that due to the oviduct's narrow anatomy and its thicker fluid content, spermatozoal movement is slowed down, an event that increases their contact with the oviductal mucosal epithelium [3]. Following this contact, sperms bind to the cilia found on the oviductal epithelia thereby forming the sperm reservoir. Evidence shows that sperm-oviductal binding involves carbohydrate recognition, where carbohydrates such as fucose found on the surface of the oviductal epithelium bind to fucose-binding molecules on the surface of sperm [6]. The seminal plasma (SP) protein PDC-109 (also called BSP-A1／A2) has been identified as this fucose-binding molecule, which is a protein secreted by the seminal vesicles that form the constituent of the SP [7]. Conversely, sperm release from the reservoir involves loss or modification of PDC-109 from the surface of capacitated sperm enabling sperm to detach from the epithelium and pull away towards the oocytes with the aid of hyperactivation [8].

Since the discovery of carbohydrate recognition as the mechanism involved in sperm binding to and release from oviductal cells, interest in the research to further understand events surrounding sperm binding and release from the sperm reservoir increased. These factors can be broadly categorized into physiological and biochemical factors [1,9]. Sperm adhesion molecules facilitate the binding of sperm to the oviductal epithelium, which is essential for sustained sperm viability and later on, their gradual release and movement toward the site of fertilization [10].

The lack of binding to the OECs can lead to a decreased survival rate of the sperms in the oviduct [3]. Specific proteins and glycoproteins on the surface of sperm (e.g., spermadhesins) and the oviduct epithelium facilitate binding [4]. The presence of specific receptors on the oviductal epithelium and corresponding ligands on sperm is crucial for adhesion. This includes integrins, selectins, and other cell adhesion molecules [11]. Therefore, our systematic review aims to: 1) provide a comprehensive systematic assessment of the literature that used *in-vitro* models to assess the non-steroid hormone factors involved and their effects on sperm binding and release from the sperm reservoir in several animal species, and 2) to compare sex sorted versus conventional, epididymal versus ejaculated semen ability to bind to the OECs. Understanding these factors is essential for improving our comprehension on how conventional and sex sorted semen interact with the OECs and the effects on reproductive outcomes. This may aid in improving the current reproductive technologies such as timed artificial insemination (TAI), in-vitro fertilization (IVF) and managing fertility in both domestic animals and wildlife species.

2.0 Methods

In this review, all in-vitro experimental animal models investigating factors affecting sperm-oviduct interaction and met the inclusion criteria were included. Information was collected on the methodology of the model (author and year of publication, Title, objective, species of animals used, semen type, factors affecting sperm binding or release from the oviductal epithelium, oviduct model used, incubation period). The systematic review protocol for the in-vitro study could not be registered on PROSPERO following the website guidelines.

2.1 Eligibility criteria

2.1.1 Inclusion Criteria

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12] were followed in this systematic review. Articles that met the following criteria were included; studies regarding sperm-oviduct interaction, in-vitro experimental animal models conducted between 1st January 1990 and 31st July 2024. The population, intervention, comparison, outcome and study design (PICOS) was followed. (1) population – all in-vitro animal experimental studies assessing factors affecting sperm-oviduct interaction (2) intervention – Any non-steroid hormone intervention affecting sperm binding and release (3) comparison – oviduct cells not treated or any other control (4) outcome- effect of intervention, either inhibits sperm binding or enhances sperm binding to the OECs (5) study design – in-vitro experimental studies assessing sperm-OECs interaction investigating sperm release and binding to the OECs.

2.1.2 Exclusion Criteria

Studies were excluded from the comprehensive literature review if they centered on in-vitro studies involving samples from humans, birds and fish, focused on other outcomes other than sperm binding or release from the OECs, steroid hormone supplemented experiments, all in-vivo experiments, reviews, letters to the editor, comments, studies not adequately translated

into English by google translator, conference proceedings and encyclopedias. Studies published before 1st January 1990 or after 31st July 2024 were also excluded.

2.2 Information sources

The three online databases Web of Science, PubMed, and Google Scholar were used to obtain the articles.

2.3 Search strategy

A thorough literature search focused on factors affecting sperm binding and release from the sperm reservoir in animal species, encompassing studies published in English and other languages that were adequately translated by google translator. One author was responsible for the search. The inclusion criteria for the search used one phrase from the databases, PubMed, Web of Science, and Google Scholar published between 1st January 1990 and 31st July 2024 which read as; (sperm oviduct interactions OR sperm reservoir OR fallopian tube OR oviduct epithelial monolayers OR epithelial explants OR epithelial spheroids AND in vitro techniques OR in vitro experiments AND sperm binding OR sperm release OR sperm density AND in-vitro fertilization AND animal models OR animal studies AND sperm survival OR sperm viability) AND (molecules OR factors) AND (sorted sperm OR sorted spermatozoa OR epididymal sperm) . In addition, the bibliography of the selected papers was critically reviewed to identify articles that the automated search could not capture. The online search in the three databases was conducted on 10th August 2024

2.4 Study Selection

The initial review assessed the titles and abstracts of the articles, and any disagreements were resolved through discussion until an agreement was established. After that, the two reviewers independently evaluated the titles and abstracts of all publications found. In the event of a dispute, a consensus was reached through discussion of which articles should be selected

for full-text review. Two researchers then independently evaluated the full texts to assess the publications' appropriateness for inclusion. Any differences between the authors were handled, with the option of discussion.

2.5 Data Extraction

Two authors conducted data extraction independently. In case of disagreements, they were resolved through discussion. Data extracted included: Title of the article, Objectives, year of publication, authors, semen type used (i.e., fresh, frozen, ejaculated or epididymal, conversional or sexed), species, sample size, factors affecting sperm binding or release from the OEC monolayers, aggregates or explants. A descriptive synthesis without Meta-analysis was applied, because of the inclusion of different methods and protocols in the studies and due to heterogeneity of the data obtained.

3.0 Results

3.1 Study selection

A total of 723 articles were found in the three online database search and 5 from back referencing. A flow chart of the literature search and study selection is shown in Figure 1. After the removal of duplicates, we reviewed 685 manuscripts. Only 46 articles met the inclusion criteria and were included in the narrative synthesis.

Figure 1. PRISMA flow diagram for the included searches of databases.

3.2 Risk of Bias Assessment

The risk of bias in the included studies was assessed using the criteria compiled by the National Toxicology Program-Office of Health Assessment and Translation (NTP-OHAT) and adapted for the evaluation of in-vitro research [13]. Two independent reviewers

evaluated the risk of bias in the included studies. When reviewers could not agree, a consensus was established after discussing. The risk of bias for each included study's had six categories assessed and entered in an Excel spreadsheet as definitely high risk, definitely low risk, probably high risk, and probably low risk and later exported to the statistical package for social sciences (SPSS) version 20 for analysis (Figure 2).

Figure 2. Risk of bias in the Included study using the NTP-OHAT tool

3.3 Quality Assessment of the Studies Included

The quality of the publications included in the review was evaluated by MCS and MC using a checklist compiled by [14] and blinded to the authors names. Assessment revealed that studies did not describe how sample sizes were statistically chosen to improve the power of the studies. Besides only one study reported blinding of investigators to the allocation of treatment during the sperm binding experiments (Figure 3).

Figure 3. Quality Assessment of the Included Studies

Table 1: Quality assessement category and Questions for Fig 3

Assessment Category	Question
I	Is the cell culture passage number reported?
II	Is the experimental unit clearly stated?
III	Replication of experiment reported?
IV	Source of cell lines provided?
V	Are cell seeding details reported?
VI	Are cell culture characteristics reported?
VII	Does article report how sample was selected to ensure adequate power?

VIII	Random allocation to groups reported?
IX	Investigators blinded to the group allocation?
X	Attrition/Exclusions reported?

3.4 Synthesis of Results

3.4.1 Biochemical factors affecting sperm release and sperm binding to the oviduct epithelial cells in in-vitro studies.

Bovine studies (Table 2) showed that sperm binding density to the oviductal epithelium was reduced by the glycosaminoglycan (GAG) heparin [15-18]. On the other hand, hyaluronic acid increased the binding ability of bull sperm to the epithelial spheroids and, there was no significant difference in the sperm binding density to the oviductal spheroids of the preovulatory or postovulatory isthmus and ampulla [15]. Likewise, [18] reported no significant difference in the number of sperm bound to isthmus and ampulla epithelia and that capacitation induced by heparin induces sperm release from the oviductal explants (OE). Besides, penicillamine enhanced sperm release from the OEC monolayers and OE [16,19]. Furthermore, the endocannabinoid anandamide (AEA) inhibited sperm binding to the OEC monolayers and OE through the cannabinoid receptor type 1 (CB1) and the transient receptor potential vanilloid type 1 (TRPV1) activation [20,21] and through the nitric oxide pathway [22]. In contrast, no effect on sperm oviduct binding and release was observed following supplementation with AEA [23].

In yet another study, fucoidan [24], fucose and fucoidan in which no region (isthmus and ampulla) effect was detected in sperm oviduct interaction [6], fucose and Lewis a-oligosaccharide dependent on calcium and in a dose dependent way [25] inhibited sperm binding to the OEC monolayers and OE. Contrastingly, N-acetyl-D glucosamine [5]

enhanced bull sperm binding to the OE. [26] found that N-acetyl galactosamine and galactose decreased Ilama sperm binding to the OE. Likewise, [27] reported that galactose inhibits the binding of equine sperm to the OEC monolayers. Moreover, the disaccharides maltose and lactose and the monosaccharide mannose reduced boar sperm binding [28] to the OEC monolayers. Furthermore, asialofentuin inhibited equine and porcine sperm binding to the OEC monolayers and to the OE [27,29,30]. Strikingly, natriuretic peptide type C increased sperm motility and intracellular calcium levels and induced the release of porcine sperm from the isthmic oviduct OA [31]. On the other hand Lewis^{x} trisaccharides [32] and 6-sialylated biantennary glycans [33] enhance porcine sperm binding to the OA.

Table 2: Description of studies assessing the effect of biochemical supplements on sperm binding and release from oviductal epithelial cells in-vitro in different animal species

Species	Chemical factor	Effect on sperm binding or release	Oviduct Model	Incubation Duration	Reference
Bovine	Heparin sulphate	Decreases binding	Spheroids	60min	Mahé et al., (2023) [15]
	Hyaluronic acid	Increases binding	Spheroids	60min	Mahé et al., (2023) [15]
	Anandamide	Enhances sperm release	Monolayers, Explants	60min	Gervasi et al., 2016) [20]
	Heparin	Enhances sperm release	Ex vivo	30min	Ardon et al.,(2016)[34]
	Heparin, Penicillamine	Enhances sperm release	Monolayers, Explants	30min	Gualtieri et al., (2013) [16]
	Anandamide	Induce sperm release	Monolayers	60min	Osycka-Salut et al., (2012) [22]
	Sulfated glycoconjugates, Penicillamine	Induce sperm release	Monolayers, Explants	30min	Gualtieri et al., (2010) [19]
	Heparin, Penicillamine, Anandamide	Heparin & penicillamine induce sperm release, Anandamide has no effect	Monolayers, Explants	30min	Talevi et al., (2010) [23]
	Heparin, Penicillamine	Induce sperm release	Monolayers, Explants	30min	Gualtieri et al., (2009) [35]

	N-acetyl-D-glucosamine, D-mannose, D-Fucose	Enhance sperm binding	Aggregates	3hr	Kon et al., (2009) [5]
	R (+) Methanandamide	Inhibits sperm binding and induce sperm release	Monolayers	15min or 60min	Gervasi et al., (2009) [21]
	Annexins	Enhance sperm binding	Explants	30min	Ignotz et al., (2007) [36]
	Penicillamine, Beta-Mercaptoethanol, Cysteine, Dithiotreitol	Induce sperm release	Monolayers	30min	Talevi et al., (2007) [37]
	BSP-A3 and BSP-30-kDa	Increase binding of epididymal sperm and inhibits binding of Ejaculated sperm.	Explants	15min	Gwathmey et al., (2006) [38]
	PDC-109	Enhance epididymal sperm binding to the level of ejaculated sperm.	Explants	15min	Gwathmey et al., (2003) [8]
	Heparin	Induce sperm release	Monolayers	2hr	Bosch et al., (2001) [17]
	PDC-109	Inhibits sperm binding	Explants	15min	Ignotz et al., (2001) [39]
	heparin and fucoidan	Inhibits sperm binding and triggers sperm release	Monolayers, Explants	1hr	Talevi & Gualtieri (2001) [24]
	Lewis a-oligosaccharide, Fucose	Inhibits sperm binding	Explants	15min	Suarez et al., (1998) [25]
	Fucose and Fucoidan	Reduce binding density	Explants	15min	Lefebvre et al., (1997) [6]
	Heparin	Reduce binding density	Explants	15min	Lefebvre et al., (1996) [18]
Camelid	N-acetyl galactosamine and galactose	Decreases sperm binding	Explants	1hr	Apichela et al., (2010) [26]
	Presence of sperm-binding agent	Enhance sperm binding	Explants	1hr	Apichela et al., (2009) [40]
Equine	Galactose,	Reduces sperm	Monolayers	95min	Dobrinski et

	Asialofentuin	binding			al., 1996a) [27]
Porcine	Natriuretic peptide type C	Facilitates release	Aggregates	30min	Wu et al., (2023) [31]
	Caudal epididymal components	Enhances ejaculated sperm binding	Explants	15min	Pena et al., (2015) [41]
	Lewis X trisaccharides	Enhance binding	Aggregates	15min	Machado et al., (2014) [32]
	6-sialylated biantennary glycans	Enhance sperm binding	Aggregates	15min	Kadirvel et al., (2012) [33]
	Spermadhesin AQN1	Inhibits sperm binding	Explants	15min	Ekhlasi-hundrieser et al., (2005) [42]
	Glycoproteins asialofetuin and ovalbumin	Inhibits sperm binding	Explants	15min	Wagner et al., (2002) [29]
	Disaccharides Maltose, Lactose and monosaccharide Mannose	Reduce sperm binding	Monolayers	30min	Green et al., (2001) [28]
Equine	Glycoprotein asialofetuin and its terminal sugar galactose	Inhibits sperm binding	Explants	50min	Lefebvre et al., (1995) [30]
Hamster	Fetuin and its terminal sugar, N-acetylneuraminic acid	Inhibits Epididymal sperm binding	Ex vivo oviduct	15min	Demott et al., (1995) [43]

PDC 109 (Protein Disulfide Isomerase); BSP (Bovine Seminal Plasma)

3.4.2 Effect of Biochemical supplementation to ejaculated and epididymal semen on sperm-oviduct interaction.

It has been reported that the binding ability of boar spermatozoa develops in the epididymis and that caudal EP components enhance boar sperm binding to the OE [41]. In this study, the binding of EJ spermatozoa to porcine isthmus was higher than that for caudal EP spermatozoa, and EJ boar sperm attached to the isthmus than ampulla epithelium. Interestingly, the SP protein PDC-109 [39] inhibited bull EJ sperm binding to the OE whereas PDC-109 enhanced bull EP binding to the level of EJ [8]. Strikingly, [38] reported

that BSP-A3 and BSP-30-KDa increased binding of bovine EP but inhibited binding of EJ to the OE. Likewise, the protein annexin was reported to enhance bovine EJ sperm binding ability to the OE [36]. These proteins bind to the sperm membrane and are involved in sperm capacitation, which is required for successful fertilization [44]. Furthermore, [19] reported that sulfated glycoconjugates and penicillamine are potent inducers of bovine EP sperm release from the oviductal epithelium. In this study EP were able to bind to the oviductal epithelium at a lower extent than frozen-thawed EJ. Likewise, fetuin and its terminal sugar, N-acetylneuramic acid inhibited hamster EP sperm binding to the oviductal epithelium [43].

3.4.3 Biotechnological process affecting sperm-oviduct Interaction

3.4.3.1 Effect of semen sorting

In the bovine study conducted by [3], it was reported that the mechanical, chemical and time stress of semen-sorting reduces sperm binding to the ampulla oviduct epithelium (Table 3). In this study sex-sorting caused abnormal movement patters, deformations of the sperm heads, sharp bends in the tails and a high prevalence of damaged mitochondria. Likewise, [45], reported plasma membrane destabilization and capacitation like changes due to sex-sorting of bull semen in which the XY sorted sperm bound at a lower rate to the OE than non-sorted semen after 24 hours of incubation. Further, [46], reported that the sex-sorting process of boar spermatozoa alters motility and plasma membrane adhesion receptors for the oviduct which decreases sperm binding to the OA. In agreement with bovine studies reporting reduced sexed sorted semen binding to the OECs [3,45], [47] reported a decreased binding of sperm to the OEC monolayers in ovine species due to sex-sorting of semen. In contrast, [48] did not find any differences between the number of sex-sorted and non-sorted sperm bound to the oviductal cells.

3.4.4 Physiological processes affecting sperm-oviduct interaction

It has been reported by [49] that bull spermatozoa with high mitochondria membrane potential and low tyrosine phosphorylation enhances sperm binding to the OE. Similarly, reduced or absent tyrosine phosphorylation enhanced boar sperm binding to the OEC monolayers [50] whereas tyrosine phosphorylation status of equine sperm [51], non-phosphorylated canine sperm heads [52,53] enhanced sperm binding to the OE and OEC monolayers. On the other hand, high levels of protein phosphorylation inhibited boar sperm binding to the oviductal epithelium [54]. In addition, bull sperm with low DNA fragmentation index enhanced binding to the OE [55] whereas low calcium concentration of sperm enhanced stallion and boar sperm binding to the OEC monolayers [50,56]. Further, bulls with a β-defensin haplotype, had a higher density of sperm bound to the oviductal explants than bulls without the haplotype [57].

Table 3: Description of studies assessing the effect of biotechnological and physiological processes affecting sperm binding and release from oviductal cells in-vitro in different animal species

Species	Biotechnological/ Physiological factor	Effect on sperm release or binding	Oviduct Model	Incubation duration	Reference
Bovine	DNA fragmentation Index (DFI)	Low DFI enhances binding	Explants	30min, 1hr, 2hr	Nag et al., (2021)[55]
	Sex sorting	Reduces binding	Ex vivo	45min	Camara Pirez et al., (2020) [3]
	Sex sorting	XY bound less than non-sorted	Explants	30min, 24hr	Carvalho et al., (2018) [45]
	Mitochondria membrane potential (MMP) of sperm	High MMP enhances sperm binding	Explants	4hr	Saraf et al., (2017) [49]
	Tyrosine phosphorylation status of sperm	Low tyrosine status enhances sperm binding.	Explants	4hr	Saraf et al., (2017) [49]

	β-defensin haplotype	Enhances binding	Explants	30min	Whiston et al., (2017) [57]
Porcine	Sex sorting	Decreases binding	Aggregates	15min	Winters et al., (2018) [46]
	Protein tyrosine phosphorylation	high levels of protein tyrosine phosphorylation inhibit binding	Monolayers, Ex vivo	1hr	Luno et al., (2013) [54]
	Reduced/absent tyrosine phosphorylation of membrane proteins	Enhance sperm binding	Monolayers	3-180min	Petrunkina et al., (2001b) [50]
	Decreased cytosolic Ca2+ concentration	Enhance sperm binding	Monolayers	3-180min	Petrunkina et al., (2001b) [50]
Equine	Low calcium concentration	Enhance binding	Monolayers	6hr	Dobrinski, Suarez, et al., (1996b) [56]
	Tyrosine phosphorylation status of sperm	Enhance sperm binding	Explants	2hr	Leemans et al., (2014) [51]
Canine/ Porcine	Non-tyrosine phosphorylated sperm heads. Higher tyrosine phosphorylation of sperm tail proteins	Enhance sperm binding	Explants	3-360min	Petrunkina et al., (2004) [52]
	Non-phosphorylated sperm heads	Enhance sperm binding	Monolayers	3-360min	Petrunkina et al., (2003) [53]
Ovine	Sex sorting	No effect on binding	Monolayers	2hr	De Graaf et al., (2006) [48]
	Sex sorting	Reduce sperm binding	Monolayers	4hr	Hollinshead et al., (2003) [47]

4.0 Discussion

This review highlights important aspects of sperm oviduct interaction, particularly those pertaining to sperm binding and release from the OECs in animal species. It has been reported that only sperm of superior quality [37] and normal morphology binds to cilia by

their head to the OECs (58). Our synthesis strengthens the findings that have shown that the carbohydrates and their derivatives mannose, fucose, N-acetyl-D glucosamine [5], 6-sialylated biantennary glycans [33], and lewis^{x} trisaccharides [32] enhance sperm binding to the OA. However, it was reported in some studies that the carbohydrates and their derivates including fucose and lewis a-oligosaccharide [25], mannose, maltose and lactose [28], galactose [27], galactose and N-acetyl galactosamine [26,30] decreased the binding ability of sperm to the oviductal epithelium. These differences which may be due to different species employed in the studies, justify the need to assess the impact of the effect of the carbohydrates on sperm binding and/or release from the oviductal epithelium in a variety of species to design species-specific protocols to improve semen-sorting and IVF outcomes. As the sperm capacitation process begins before ovulation, the composition of carbohydrates on the sperm surface changes, limiting their capacity to adhere to the oviductal epithelium and allowing them to proceed to the oocyte [59]. This phenomenon helps to improve the chances of successful fertilization in-vivo [59]. Therefore, the use of sperm-oviduct in-vitro experiments, may aid in the selection of high-quality sperm following supplementation with carbohydrates and their derivatives.

The SP proteins PDC-109, BSP-A3, and BSP-30-kDa increased the binding ability of EP sperm to the OE. This suggests that the addition of these proteins to EP sperm can improve their fertilizing potential by enhancing various aspects of sperm function [8,44]. Therefore, the supplementation of SP during sperm-OEC co-culture may be used as a selection technique of good quality sperm to improve IVF rates. It has been demonstrated that recovery of sperm from the caudal epididymis of animals can be achieved after the slaughter of male animals, or the unexpected death of genetically highly valuable animals and for the preservation of endangered species [60]. Thus, SP proteins can be added to EP sperm to

improve its fertilizing potential in sperm-OEC co-cultures. Strikingly, improved pregnancy outcomes have been reported in women exposed to SP around the time of ovum pick up (OPU) and embryo transfer (ET) [61]. Similarly, the conception and farrowing rates were higher sows and gilts that received insemination using sperm diluted in SP [62]. Besides, proteins in SP have been positively related to sperm swimming velocity and hyperactivation, which are required for successful fertilization [63]. Indeed, supplementation of SP in sperm-OEC co-cultures may provide good models to improve the fertilizing ability of the sperm released from the oviductal epithelium that may later be used in IVF programs to improve outcomes. However, SP proteins inhibited EJ sperm binding to the OE [38]. Likewise, the addition of SP failed to improve post-thaw sperm quality in the buck and ram [64,65]. This warrants further research to clarify the factors and mechanisms that enhance sperm binding and/or release from the oviductal epithelium after treatment of sperm with these proteins. Additionally, proteins in SP bind to the sperm plasma membrane during ejaculation, thereby promoting sperm interaction with the OECs and enhance sperm fertilizing ability [66]. These factors can contribute to enhanced ARTs by optimizing conditions for sperm selection, capacitation, and fertilization using sperm-OEC co-cultures [67]. The supplementation of the glycoproteins fetuin and its derivative asialofetuin in sperm-OEC co-cultures can aid in the selection of the most viable and motile sperm for fertilization, hence enhancing the quality of sperm utilized in ART procedures [68].

The tyrosine phosphorylation status of sperm plays an important role in their ability to bind to the oviduct and their subsequent fertilizing potential [50,54]. Our finding showed that sperm bound to the oviduct epithelium had lower levels of tyrosine phosphorylation, implying that the binding process could be a mechanism for selecting sperm with optimal tyrosine phosphorylation levels essential for successful fertilization [54] and can be used to improve

IVF success rates [69,70]. Therefore, sperm-OEC co-cultures maybe used as alternative methods in the selection of sperm with high fertilizing ability to improve IVF rates. Further, the ability of the sperm to interact with and penetrate the oocyte is strongly associated with the tyrosine phosphorylation of proteins in the sperm head. This alteration improves the sperm's ability to bind to the zona-pellucida of the oocyte, which promotes optimal fertilization [71]. Furthermore, ensuring optimal tyrosine phosphorylation is crucial. It aids in the selection of sperm that are fully capacitated and capable of successful fertilization [72].

Sperms must be released from the isthmic oviductal cells and migrate towards the ampulla section of the oviduct. Here, we have gathered and synthesized evidence that supports the importance of certain molecules in sperm release from oviductal cells. Notably, GAGs such as heparin and fucoidan and the thiol-reducing agents penicillamine, mercaptoethanol, cysteine, and dithiotreitol have been shown to play a fundamental role in inducing sperm release from the sperm reservoir. The presence of GAGs ensures that only capacitated and motile sperm gets released, hence increasing the odds of fertilization [24]. This underpins the importance of the sufficient production of GAGs from the oviduct following the ovulation signal to induce capacitation-like changes in sperm. These changes are key to facilitating sperm release from the sperm reservoir and affect the fertilizing potential of sperm. In a study conducted by [73], the supplementation of GAGs to sperm improved the kinematic parameters of sperm, increased the levels of capacitation and acrosome reacted sperm thereby improving the in-vitro fertilizing ability of sperm, embryo development rates and embryo quality and increased the total blastocyst cell number at day 8 after IVF. In-vitro, the thiol-reducing agents induce sperm release from the oviduct epithelium by modulating the redox status of sperm surface proteins [37]. This involves the reduction of disulfide bonds on the surface of sperm leading to the selection of high-quality and capacitated sperm able to

fertilize oocytes [35,37]. Interestingly, the levels of sulphhydryls in sperm-surface proteins were low in sperm that bound to OECs, high in sperm that was unable to bind and markedly elevated in released sperm [35] .These thiol-reducing compounds have been reported to be present in the oviductal fluid in different species, and their concentration increases during oestrus [24,35,37,74-76] Overall, understanding mechanisms that govern sperm release from oviductal cells are critical as they are associated with the selection of high-quality and capacitated sperm with high oocyte fertilizing potential [55].

Another group of compounds found in oviduct of mammals that induce sperm release from the OECs are the endocannabinoids [23,77,78] Also, the oviduct is capable of synthesizing and regulating the concentrations of endocannabinoids along the isthmus and ampulla [23]. Notably, AEA and methanandamide (Meth-AEA) induce sperm release from the oviduct epithelium by activating the nitric oxide pathway during sperm capacitation [22]. Furthermore, AEA was reported to induce sperm capacitation through the activation of the CB1 and TRPV1 [78] thereby impacting the fertilizing potential of sperm. A different result was reported in an in-vitro study in which AEA had no effect on sperm oviduct release and binding [23]. In a study involving human semen, it was reported that AEA may affect IVF of sperm by modulating motility, capacitation, and acrosome reaction [79]. Interestingly high amounts of AEA were found in human seminal plasma [80,81] while fluctuating levels of AEA were found during the estrus cycle in the bovine oviduct [82]. Therefore, understanding the role of the endocannabinoid system in the regulation of mammalian male fertility may provide valuable insights for improving IVF protocols and other ARTs using sperm bound to and later released from the oviductal epithelium. Similar to the steroid hormone in-vitro studies in which sperm bound to the OEC and then released by progesterone showed high IVF outcomes [83,84], these non-steroid factors may be alternatives to the selection of high-

quality sperm following sperm-OEC co-cultures to improve IVF success rates.

Inhibiting undesired sperm from binding to the OECs can lower the risk of complications while also improving the overall safety and efficacy of ART operations. Remarkably, inhibiting excessive sperm binding can help prevent polyspermy and ensure that only the best sperm are involved in fertilization, thereby enabling the development of better embryos [85]. For example, glycoconjugates can prevent poor quality sperm from adhering to the oviductal epithelium [24]. Consequently, by comprehending the factors inhibiting sperm binding to the OECs, specific protocols that optimize conditions for fertilization and embryo development can be established. Notably, the strategic application of factors that inhibit sperm from binding to the OEC can improve the effectiveness and success rates of IVF through the selection of superior sperm following sperm-OEC co-cultures. On the other hand, sperm binding to the OEC allows for a gradual release of sperm before ovulation *in-vivo* thereby reducing the chances of polyspermy to ensure normal embryonic development [86].

To date, semen sorting has been reported to alter motility, plasma membrane adhesion receptor for the oviduct, membrane destabilization, and capacitation-like changes in mammalian sperm [87,88]. However, the modified sex-sorted sperm behavior, mechanisms, and processes to improve the binding ability of sex-sorted semen to the OEC need further investigation if the conception rates using sex-sorted semen both in-vitro and in-vivo are to be improved. Our finding showed that sex sorting reduced the ability of sperm to bind to the oviductal ductal epithelium. The XY-bearing sperm showed a lower binding ability to the oviductal epithelium compared to non-sorted sperm. This was due to a high proportion of sexed sperm with destabilized plasma membranes [45], a possible indicator of induction of the capacitation-like process and acrosome reaction due to sex-sorting [88,89] thus reducing

the binding ability of sexed sperm to the oviductal epithelium. Therefore, understanding the sperm structural changes due to the sorting process may help to deduce methods to mitigate these effects. This may enhance the viability of sexed sperm and improve its binding ability to the OECs during the formation of the sperm reservoir leading to increased conception rates following AI in-vivo and increased IVF rates. Blastocyst rates of about 45% have been reported in in-vitro embryo production (IVP) procedures using sexed sperm [90]. Nonetheless, many studies found the mean blastocyst rates to be approximately 25% [91-94], implying that improvements to the sorting process is required. In addition, understanding the impact of OEC bound and later released sexed sperm in IVF programs may aid in elucidating factors affecting sorted sperm binding to the oviductal epithelium and the effect on fertilizing potential of released sperm.

5.0 Limitations

The study has the following limitations. Different methods were used in the studies, which were composed of various components that may affect sperm binding and release differently. Some studies used spherical everted vesicles (epithelial spheroids or explants) while others used monolayers and ex-vivo oviducts, this may affect the determination of sperm binding density and the conclusions derived from the studies. Monolayers are flat, single layers of cells that provide a two-dimensional environment that make it easy to determine sperm binding density but may not fully replicate the in-vivo conditions. Moreover, monolayers usually lose their ciliation and secretory activity leading to unspecific sperm binding [58] thereby making it difficult to compare with sperm bound to oviductal spheroids.

On the other hand, epithelial spheroids offer a more realistic model for sperm binding as they mimic the three-dimensional structure of the oviduct leading to more accurate insights into how sperm interact with the oviductal epithelium in a natural setting. However, OE are

typically heterogenous in shape and size and difficult to standardize among replicates leading to a rough estimate of the binding surface and number of bound sperm [72]. Besides, these in-vitro systems lack the natural flow and turbulence of oviductal fluids that may interact with several factors on the sperm and oviduct to mediate the sperm-oviduct interactions. This makes it difficult to correlate the in-vitro results to in-vivo fertility. Further, there are limited publications assessing sex-sorted semen oviduct interactions and wildlife species sperm-oviduct interactions. We suggest that subsequent in-vitro experiments should focus on improving the methodological quality of the studies for purposes of improving the power of the studies through appropriate sample size determination, random allocation of samples to experimental groups and ensure that investigators are blinded to the group allocation during the experiments or when assessing outcome.

6.0 Conclusion

Our synthesis suggests that factors affecting sperm binding and release from the ampulla and isthmus segments of the oviduct in different species includes but not limited to sex-sorting, glycoproteins, GAGs, carbohydrates and tyrosine phosphorylation. These factors either reduce or increase the binding density of sperm to the OECs and influence outcomes of ARTs.

7.0 Future Perspectives

To improve semen-sorting and IVF outcomes, further research needs to focus on the specific effects of SP addition on conventional and sex-sorted sperm binding or release and their effects on IVF success rates. Since the SP is composed of several components, specific molecular factors and mechanisms must be investigated that enhance sperm binding and/or release from the isthmic and ampullary OECs. We also suggest that protective molecules that

may enhance the binding ability of sex-sorted spermatozoa be studied. Additionally, comparing several species to find shared and distinct sperm binding and release processes is required. This can enhance methods for breeding animals and shed light on evolutionary adaptations. Furthermore, there is a need to study multiple species by using more heterologous systems as using epithelial cells and sperm from one species may not be directly applicable to other species thus limiting the generalizability of the findings. Furthermore, new insights into sperm physiology may become apparent due to a better understanding of how the oviduct environment including, pH and ion concentration affects sperm-oviduct interaction.

It may be interesting to investigate the effect of sex-sorting on the synthesis of oviductal glycoproteins and acid mucopolysaccharides in the isthmic portion of the oviduct because the functional sperm reservoir forms in this segment following insemination. There is further a need to assess and clarify the sperm head protein and molecule composition alteration on the sperm head following the sorting process because these proteins are important in mediating sperm binding to the tubal epithelium. Besides, there is a need to assess the effectiveness of calcium signaling cascades following the sex-sorted sperm binding to the oviduct epithelium in different animal species. Likewise, future studies should focus on critically investigation the exact timing and molecular mechanisms involved in GAG production in different species, this may aid in devising treatment protocols to improve ARTs such as TAI. To increase wildlife populations and preserve endangered species through ARTs, future studies must also assess factors affecting sperm-oviduct interaction in wildlife species. Thus. the success rates of IVF could be increased by evaluating how these processes are affected by the interaction of sperm and OECs. The results derived from such studies may also be used to improve the in-vivo outcomes during AI programs.

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9.0 Conflict of Interest

The authors declare that no competing interests exist.

10.0 Author Contributions

MCS Roles: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing-Original draft, Writing-review and editing.

MC Roles: Methodology, Investigation, Writing-review and editing.

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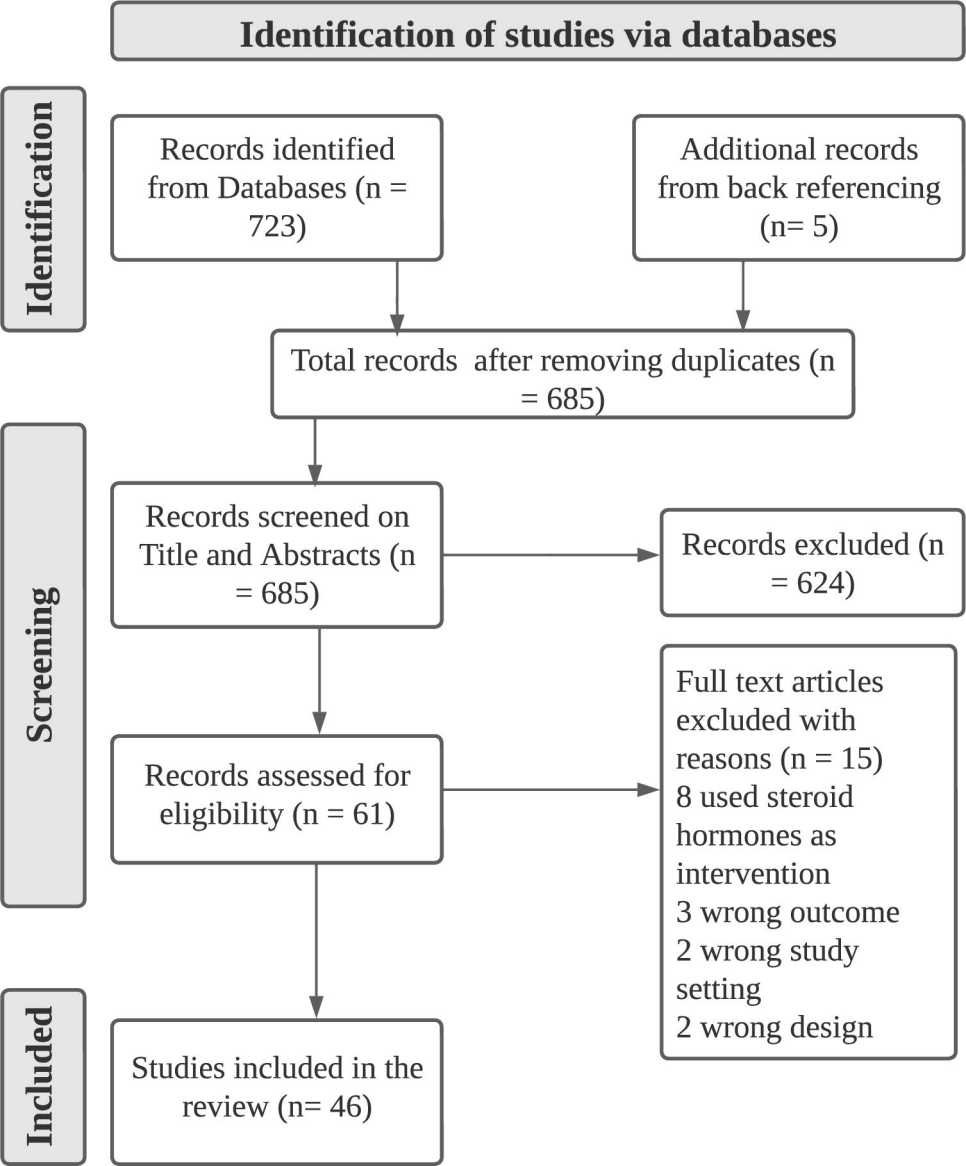
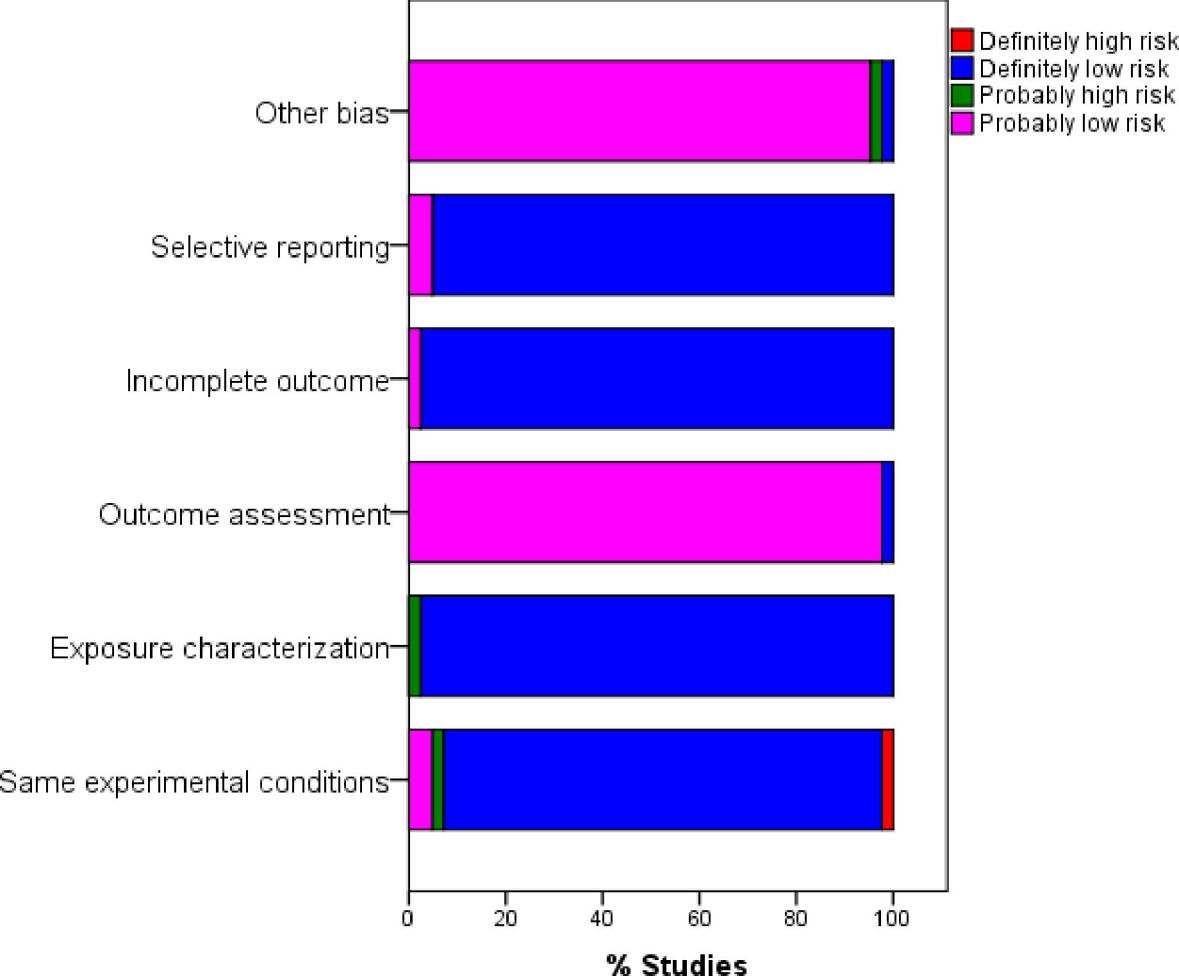
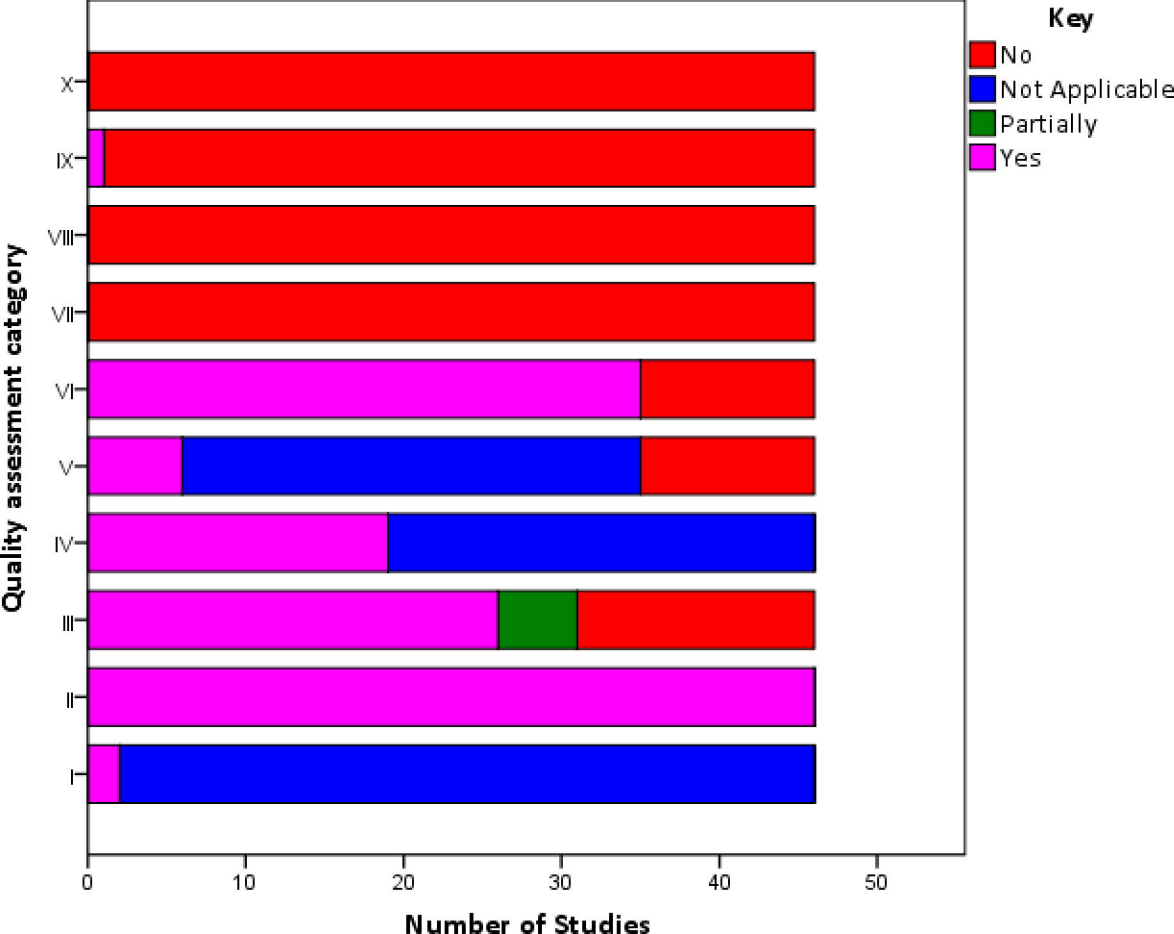

Identification of studies via databases
Identification
Records identified from Databases (n = 723)
Additional records from back referencing (n= 5)
Total records after removing duplicates (n = 685)
Screening
Records screened on Title and Abstracts (n = 685)
Records excluded (n = 624)
Records assessed for eligibility (n = 61)
Full text articles excluded with reasons (n = 15)
8 used steroid hormones as intervention
3 wrong outcome
2 wrong study setting
2 wrong design
Included
Studies included in the review (n= 46)


Definitely high risk
Definitely low risk
Probably high risk
Probably low risk
Other bias
Selective reporting
Incomplete outcome
Outcome assessment
Exposure characterization
Same experimental conditions
0
20
40
60
80
100
% Studies


Key
No
Not Applicable
Partially
Yes
Quality assessment category
X
IX
VIII
VII
VI
V
IV
III
II
I
0
10
20
30
40
50
Number of Studies