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Contact Spermicides as Contraceptives: Efficacy and Current Status

P. R. REDDY, A. SHARMA, S. GUPTA AND A. K. TIWARY*
Department of Pharmaceutical Sciences and Drug Research,
Punjabi University, Patiala-147 002.

Contact spermicides represent a novel method of contraception. Many compounds with diverse pharmacological activity have been evaluated *in vitro* for their spermicidal activity. Drugs with membrane stabilizing action such as procainamide, quinidine, mexiletine, propranolol, certain ionophores, chelating agents such as EDTA, gramicidin, natural or synthetic surfactants such as saponins, nonoxynol, benzalkonium chloride, anti-liquefying agents have all been demonstrated to possess good spermicidal activity. However, there is a paucity of data regarding the safety profile of most of these agents. In case of propranolol, chlorhexidine, gossypol and nonoxynol where such data is available, the results are not worthy enough to recommend their widespread use. Nonoxynol is the only contact spermicide currently being employed clinically. Combination formulations of two or more contact spermicides are being evaluated in order to minimize their adverse effects. But there is still a need to develop more safe contact spermicides.

Efficient methods of contraception are the only solution to check the growing global population. Many methods such as condoms, oral contraceptives and intrauterine devices are available since long but there is still a quest for alternative means. Development of contact spermicides represents a novel approach in this direction. Contact spermicides are defined as drugs that have the ability to immobilize, kill or incapacitate the sperm upon contact. These drugs may have a better patient compliance and can additionally protect the vagina from microbial infections.

Post ejaculatory modulation of sperm functions:

Contact spermicides are designed to act on sperm once they are deposited in vagina after ejaculation. Therefore, to understand the target site of these drugs it will be imperative to study the sperm function after ejaculation. Calcium binding substances and calcium transport inhibitors are secreted by male accessory sexual organs and mixed with sperm during ejaculation[1]. Subsequent to ejaculation, cholesterol is removed from the acrosomal membrane thereby making it more fluid. Progesterone present in fallopian tubes opens calcium channels present in sperm membrane, thereby causing a calcium influx[2]. Furthermore, calcium removes water molecules and neutralizes the anionic charge of the lipid membrane. This step is necessary for migration of molecules involved in sperm-egg fusion[3,4]. This acrosome reaction is an essential prerequisite for fertilization. *In vitro*, human sperm looses its capability to penetrate the oocytes in calcium-free medium which is regained upon addition of 1.21 mM calcium[5]. The process of membrane fusion is an active process and is triggered by a temporal displacement of membrane bound calcium and ATP. This induces a transient destabilization of the membrane that makes membranes capable of fusing with each other[3]. Although, calcium is essential for fertilization, an increase in intracellular calcium is probably the main cause of sperm death.

*For correspondence
e-mail: aktiwary@rediffmail.com

Properties of an ideal contact spermicide:

To be an effective contraceptive agent, a compound must meet the following requirements:

a) It should immediately and irreversibly produce incapacitation/immobilization of the sperm.

b) It must be non-irritating to the vaginal and penile mucosa.

c) It should not have adverse effects on the developing foetus.

d) It must be free from long-term topical and systemic toxicity.

e) Ideally it should not be systemically absorbed. Even if it is absorbed, the peak plasma levels should be lower than that required to elicit its own pharmacological action.

f) The effectiveness of a vaginally delivered contact spermicidal agent is controlled by several factors, such as, release of spermicide from the dosage form, distribution of the spermicide in the vagina, removal or displacement of the spermicide by the coital act and interaction of vaginal fluids with the spermicide. Hence, the spermicidal formulation should be critically evaluated for these aspects.

CONTACT SPERMICIDES WITH THERAPEUTIC POTENTIAL

Many contact spermicides are at various stages of preclinical and/or clinical development. They can be broadly classified on the basis of their mode of action as shown in Table 1.

Spermicides acting through pH modification:

The spermatozoa are motile between pH 6.7 to 8.5[6]. Therefore, one of the oldest approaches for achieving contact spermicidal action has been to modify vaginal pH. Investigations on the spermicidal activity of douches of various marketed Cola drinks demonstrated that colas with an adjusted pH of 2.4 exhibited maximum spermicidal activity[7,8]. It is noteworthy that the normal pH of vaginal secretion ranges from 3.5 to 5.0. This optimum acidic pH is essential for the growth of normal microflora and for the prevention of invasion of the genital tract by pathogenic organisms. Therefore, this approach for spermicidal action does not seem to be of much clinical relevance.

Spermicides with membrane stabilizing activity:

Drugs belonging to diverse therapeutic classes but possessing membrane stabilizing activity have been shown to exhibit spermicidal action. These drugs immobilize sperm by acting on its membrane in a manner analogous to local anaesthetics. Local anaesthetics such as procainamide, quinidine and mexiltine have been demonstrated to possess spermicidal activity[9]. At μM concentrations, diltiazem and verapamil exert predominantly calcium channel blocking activity and stimulate sperm motility. On the other hand, mM concentration of these drugs produces membrane stabilizing effect and inhibits sperm motility[10]. Propranolol, a b-blocker, is also reported to possess a marked spermicidal activity. However, it is interesting to note that the purified D-isomer of propranolol is as effective as the racemic mixture[11-14]. The fact that D-propranolol does not possess any b-blocking property, suggests that the sperm immobilizing effect of propranolol resides in its membrane stabilizing activity rather than its b-blocking activity. Propranolol-induced decrease in sperm motility is accompanied by an increased intracellular calcium[15]. Vaginal insertion of 80 mg propranolol tablet produces a fall in systolic blood pressure, heart rate and forced expiratory volume[16]. Therefore, systemic absorption of propranolol from vaginal mucosa may impede its use as a contact spermicide.

Ionophores:

Ionophores are compounds which form lipid soluble complexes with specific cations and act as vehicles for transporting these cations across biological membranes. A23187, a calcium ionophore[17,18] is reported to decrease sperm motility in a dose dependent manner with an IC_{50} value of 20 μM[19,20]. Nigeracin is a potassium ionophore and exchanges extracellular hydrogen for intracellular potassium thus producing an intracellular pH drop which is accompanied by a potent sperm immobilization action. Nonactin, is another potassium ionophore, but lacks any sperm immobilizing action[21]. This observation tentatively suggests that modulation of intracellular pH rather than intracellular potassium may be more important regulator of sperm motility. m-Chlorocarbonyl cyanide phenylhydrazone (CCCP), is a proton ionophore that eliminates potential difference across mitochondrial membrane and acts as uncoupler of oxidative phosphorylation to inhibit ATP synthesis[20]. Another compound, oligomycin is not an ionophore, but it inhibits mitochondrial ATP synthesis in sperm[22]. Both these agents do not act as a spermicidal, thereby implicating the relative lack of participation of oxidative phosphorylation in normal sperm function. However, local effects of ionophores on vaginal tissue and their systemic effects after absorption are yet to be evaluated clinically.

Spermicides with surface active property; Natural surface active agents:

All surface active agents act mainly through their abil-

TABLE 1: CLASSIFICATION AND EFFICACY OF CONTACT SPERMICIDES.

S. No.	Category	Spermicidal Efficacy			Ref. No.
		Conc. Reqd.	Specimen	Time Reqd.	
I.	**pH Modifiers**				
	Sodium chloride*	> 0.2%			6
II.	**Membrane Stabilizers**				
	Diltiazem	1.4 mM#	Total semen	120 min	10
	Propranolol	5.0 mM^	Spermatozoa	1 min	15
	Verapamil	0.8 mM#	Total semen	120 min	10
	Xylocaine	16 mM#	Total semen	120 min	10
III.	**Ionophores**				
	A 23187	0.02 mM#	Total semen	120 min	20
	Nigeracin	0.008 mM#	Total semen	120 min	20
IV.	**Surface Active Agents**				
	Natural (Saponins)				
	Sapindus mukorosii	0.05%^	Spermatozoa		23
	Mollugo pentaphylla	300 µg/ml^	Spermatozoa	60 min	26
	Phytolacca dodecandra	500 µg/ml^	Total semen	3 min	27
	Calendula officinalis	500 µg/ml	Total semen	3 min	27
	Acacia auriculiformis	350 µg/ml^	Total semen	20 s	29
	Synthetic Surfactants				
	Nonoxynol-9	500 µg/ml^	Spermatozoa	1 min	15
	Compound-741	125 µg/ml	Total semen	20 s	41
	Benzalkonium chloride	0.007%^	Spermatozoa	4 min	45
	CPC	0.1%^	Spermatozoa	4 min	48
	CTAB	0.1%^	Spermatozoa	4 min	48
	Menfegol	69.4 µg/ml#	Total semen	4 min	36
V.	**Chelating Agents**				
	EDTA	5 mg/ml^	Total semen	2 min	53
	EGTA	5.5 mg/ml^	Total semen	2 min	53
VI.	**Antibacterial / Anti STD etc.**				
	Chlorhexidine	4.81 mg/ml^	Total semen	20 s	54,55
	Cytochalasin E	1 µg/ml^	Spermatozoa	30 min	63
	Magainin A	2-3 mg/ml^	Total semen	20 s	69

	AZT	0.005 mM#			70
	NNIS (F-PBT)	0.147 mM#			73
VII.	**Other Approaches**				
	a-Chlorohydrin	0.1 mM^	Spermatozoa	15 min	74,75
	Mercury	2.7 mg/ml			80
	Nitrophenols	6.9 mg/ml			80
	Zinc sulfate	1%^			80
	Gossypol	40 mg/ml^	Total semen	20 s	86
VIII.	**Miscellaneous**				
	Enalapril	20 mM^			82
	Cholic acid	1.25%			83
	Zinc acetate	1%^	Total semen	30 s	91
	Aloe barbedensis (lyophilized)	10%^	Total semen	30 s	91
	S-11	0.02 mg/ml			81
	Imipramine	0.16 mM#	Total semen	120 min	106
	Quinine	0.1%^	Spermatozoa	30-60 min	48
	Emetine	0.1.%^	Spermatozoa	30-60 min	48

Table summarizing few contact spermicides and their spermicidal concentration. *Indicates that the compound is spermiostatic and not spermicidal, # indicates the EC_{50} value and ^ indicates the EC_{100} value of the compound. It is important to note the sample used for testing (total semen or spermatozoa separated from semen) the efficacy of the compounds.

ity to lower interfacial tension thereby causing loss of membrane integrity of sperm. Saponins are ubiquitously occurring natural surfactants. Among the various saponins evaluated, those isolated from *Sapindus mukorosii* (reetha) have shown most potent spermicidal activity. Spermicidal activity of this plant is mainly due to the saponins containing the b-amyrin (C-28) carboxylic acid type of structure such as hederagenin, oleanolic acid and basic acids[23,24]. These saponins produce morphological changes in spermatozoa characterized by vacuolation, vesiculation, disruption and erosion of the membrane which are mainly attributed to their detergent effect[23]. Saponins also increase lipid peroxidation of the sperm's mitochondrial sheath. This action can also contribute to their spermicidal effect because exogenous addition of lipid peroxides is reported to produce sperm death[25]. The ethyl acetate fraction of *Molluga pentaphylla*, a tropical herb, contains an antifungal saponin, mollugogenol-A. Mollugogenol-A exhibits dose- and time-dependent effect on sperm motility and viability, with a maximal response at 300 μg/ml[26]. Saponins isolated from *Phytolacca dodecandra* and *Calendula officinalis* have also been reported to exhibit potent spermicidal activity. The best activity against human sperm has been shown to be exhibited by lemma toxin, a trisaccharide of oleanolic acid[27]. Saponins isolated from *Acacia caesia*[28], *Acacia auriculiformis*[29] and *Acacia concinnha*[30] are also reported to possess spermicidal activity.

Saponins are naturally occurring and there is no report of their systemic toxicity. However, due to their interfacial tension reducing property they may alter the permeability of the vaginal membrane on frequent use. In addition, reduction in interfacial tension may, in fact, lead to decreased viscosity of the mucus and hence, result in an increased rate of transfer of spermatozoa through the vaginal mucosa. Therefore, it seems imperative to critically evaluate these effects before advocating the use of saponins as spermicidal agents.

Synthetic surface active agents; Non-ionic surfactants:

Octoxynol and nonoxynol are nonionic surfactants.

Nonoxynol is more potent spermicide than octoxynol. Among the different nonoxynol derivatives designated as N1-N15, N-9 (p-nonyl phenoxy polyethoxy ethanol) is reported to be the most potent spermicide[31]. The spermicidal action of N-9 resides in its ability to solubilize the sperm membrane, thereby causing rapid immobilization and cell death[32-36]. Time- and dose-dependent analysis of the effects of N-9 reveals that at a concentration of 5 μg/ml this compound has no significant effect on sperm motility. However, at a dose of 50 μg/ml it completely abolishes all sperm movement within one minute of addition[15]. In formulation of high osmolarity, a decrease in pH decreases the rate of diffusion of N-9 into cervical mucus from its solution of high concentration whereas, a decrease in pH increases its rate of diffusion from solution of low concentration[37]. This effect can possibly be attributed to the ability of N-9 to form micelles and should be critically considered while formulating vaginal gels or creams. Although, N-9 has been employed as a contact spermicide for last thirty years, there have been recent reports of vaginal irritation and lesions with its frequent use[38-41].

A compound, 741 (alkyl phenoxy polyethoxy ethanol) is used in China in place of N-9. It is also a nonionic surfactant and acts by disruption of the spermatozoan membrane structure. However, preliminary data of compound 741 in animals indicates that it has a toxicological profile comparable to that of N-9[42].

Cationic surfactants:

Benzalkonium chloride is a cationic surfactant of the ammonium series that ceases the sperm flagellar motility immediately upon contact with spermatozoa at concentrations greater than 0.007%[43-45]. Four seconds after contact, the midpiece and head are destroyed. Its spermicidal effect is accompanied by disappearance of acrosomal proteins, loss of fecundity and disturbance of the enzymes involved in carbohydrate metabolism[45]. Post-coital test and colposcopy reveals that a film containing 25 mg of benzalkonium chloride results in complete loss of sperm motility. This activity is equivalent to a sponge containing 70 mg of nonoxynol-9[46]. Benzalkonium chloride possesses a potent bactericidal and antiviral activity[47] and is routinely used as a preservative. It is interesting to note that concentration of benzalkonium required for its spermicidal action is much less than that permitted for its preservative action (0.01-0.25%).

The other cationic detergents like cetyl pyridinium chloride and cetyl trimethyl ammonium bromide are also potent spermicides and instantly immobilize the spermatozoa at a concentration of 0.1%[48]. But none of these agents is currently used as a spermicide. There are reports of histopathological and inflammatory changes in the ocular surface after one month use of benzalkonium chloride and cetyl pyridinium chloride at their preservative concentrations[49]. Therefore, changes in the permeability of vaginal membrane on continuous use of these surfactants cannot be ruled out. Moreover, these agents owe their activity to the positive charge present on them. Hence, charge neutralization by vaginal secretion, soaps and formulation additives may render them inactive.

Chelating agents:

Chelating agents are compounds that sequester divalent or trivalent metal ion to form an insoluble complex. Chelating agents such as, EDTA, EGTA and gramicidin have been reported to be spermicidal against human sperm[50]. Gramicidin completely immobilizes the sperm at a concentration of 5 μg/ml[51]. Excess calcium is detrimental to sperm motility in ejaculated human semen. Therefore, at low concentrations, EDTA and EGTA stimulate the sperm motility by chelating the extracellular calcium. However, at 5 mg/ml concentration, when extracellular calcium is decreased by approximately 65%, EDTA produces total loss of sperm motility because reuptake of calcium is prevented to such an extent that the normal functions of spermatozoa are disrupted[50]. Additionally, EDTA may impede sperm penetration into vaginal mucus. Ca^{2+} present in semen neutralizes the negative charge of sialic acid present in vaginal mucus and this reduces viscosity of the mucus. However, in the presence of calcium chelators, this interaction is prevented[52]. Chelating agents are not very promising contact spermicides because the dose required for complete immobilization of sperm motility is very high as compared to 200 μg/ml of nonoxynol-9[53]. But they may be useful in combination with other effective spermicides.

Spermicides with additional antimicrobial activity:

A contraceptive method which additionally protects against veneral infections will be of immense value. One such compound being investigated for its spermicidal action is the antiseptic, chlorhexidine. Its mechanism of spermicidal action is not fully understood. However, its antiseptic action is attributed to the high positive charge density that results in its non-specific binding to negatively charged elements on microbial cell walls. Disruption of cellular permeability, cell wall fluidity and altered metabolic activity has been suggested as a possible cause of the antiseptic

action[54,55]. Recent reports indicate systemic effects in humans following oral consumption of chlorhexidine[56-58]. Hypersensitivity to chlorhexidine upon topical use has also been reported[59,60]. Ophthalmic solutions of chlorhexidine stronger than 0.1% are irritating to the conjunctiva[61]. Hence, the use of chlorhexidine as a spermicide does not seem to be too safe.

Cytochalasins are cell permeable toxins of microbial origin and are capable of either reacting with sulfhydryl groups and preventing glucose transport (cytochalasin A) or inhibiting actin filament function without inhibiting glucose transport (cytochalasin D). All cytochalasins (A-E) are spermicides with varying potency[62]. Cytochalasin A instantly abolishes sperm motility at a concentration of 100 µg/ml while cytochalasin B has little effect on sperm motility even at concentration of 1 mg/ml[48]. Cytochalasin E significantly inhibits sperm motility at a concentration of 1 µg/ml within 30 min. Preincubation of hamster eggs with cytochalasin D (10-30 µM) is reported to significantly reduce the penetration of spermatozoa, thereby implicating the role of actin filaments in fertilization process[63].

The broad spectrum antimicrobial agent, C 31G, a mixture of n-dodecyl-dimethylamine-N-oxide (C_{12}-N-O) and N-(n-dodecyl), N-dimethyl glycine (C_{12}-butate) has also been reported to possess spermicidal action[64].

Magainins A and G are a class of simple proteins having 32 amino acids. They were initially isolated from the skin of the African clawed frog *Xenopus laevis*. They exhibit spermicidal action[65], besides antimicrobial activity[66-68]. The minimum concentration of magainin A required to immobilize spermatozoa within 20 s has been reported to be 100 µg in rat and 200 µg in humans. Magainin A is more active than magainin G[69]. Recent reports indicate that magainins exert their spermicidal effects through physical detergent mechanism.

AZT has been reported a potent spermicide[70]. Another anti HIV agent reported to be spermicidal is (5S,6R) and (5S,6S)-5-bromo-6-methoxy-5,6-dihydro-AZT-5′-(para bromo phenyl methoxy alaninyl phosphate) (WHI07). This compound has an EC_{50} value of 5 mM. This is markedly less than that of detergent spermicide N-9 (EC_{50} of 81 µM). The compound also displays a potent anti HIV activity with an IC_{50} value of 0.005 µM in HIV replication assays. This value is virtually identical to that reported for AZT[71,72].

Dcruz *et al.* synthesized novel non-nucleoside inhibitor (NNIS) of HIV-1 reverse transcriptase and examined the compounds for HIV and spermicidal activity. Among three NNIS synthesized, two potent spermicides are S-DABO and F-PBT[73].

OTHER APPROACHES

Inhibition of fructose metabolism:

Alpha chlorohydrin inhibits oxidative metabolism of fructose to carbon dioxide and exhibits a marked spermicidal activity[74,75]. The drug is a stereoselective prodrug because (R) isomer is inactive whereas the (S) isomer is oxidized *in situ* by $NADP^+$-dependent dehydrogenase to its active metabolite. (S) 3-chloroacetaldehyde. 1-Chloro-3-hydroxy acetone is another analogue that acts in an identical manner probably through its conversion to the same active metabolite[76-78].

Antiliquefying agents:

The active antiliquefying agents immediately coagulate ejaculated semen, possibly through a denaturing effect on the glycoproteins present in coagulated material[79]. Mandal and Bhattacharya have evaluated natural and synthetic enzyme inhibitors or inactivators for their antiliquefying activity. Among these, 27 demonstrated no effect, 36 quickened, 20 delayed the process of liquefaction and 18 agents stopped liquefaction completely. Highly effective antiliquefying property was exhibited by mercury (2.7 mg/ml), nitrophenols (6.9 mg/ml), sodium naphthyl phosphate, FCI-007 and tannic acid[80]. A combination of antiliquefying and a potent spermicidal agent may offer a highly promising approach towards vaginal contraception. However, the safety index of the currently evaluated antiliquefying compounds is too low to permit their use in pharmaceutical formulation for *in vivo* use.

MISCELLANEOUS AGENTS

Certain other compounds with unrelated pharmacological activity such as 4-bromo-7-hydroxy indane oxime[81], enalapril[82] and cholic acid[83] reduce sperm motility. However, their exact mechanism of action is yet to be delineated. Gossypol, a polyphenolic aldehyde extracted from cotton seed, is reported to be spermicidal agent. The concentration of gossypol required to immobilize 100% spermatozoa immediately upon contact is 40 mg/ml. The racemic mixture is as effective as the (R) and (S) isomers with respect to spermicidal activity[84]. Gossypol inhibits sperm motility possibly by increasing lipid peroxidation and finally causes membrane disintegration[85]. In addition, it exhibits antiviral and antitumor activity[86-88]. Systemic administration of gossypol in humans lowers serum potassium

level that is neither reversed by supplementation with potassium salt nor by administration of triamterene. Long term consumption of gossypol is also associated with increased SGPT and decreased IgG levels[89]. Although, no data is available regarding the absorption of gossypol from vagina, these findings indicate that gossypol may not be a safe contact spermicidal.

A bioactive peptide P20-44 obtained from a cationic antimicrobial protein (CAP 37) present on human neutrophils, is reported to cause loss of sperm motility without disruption of the acrosomal membrane[90]. Zinc acetate (1% concentration) is spermicidal, while the other zinc salts such as, zinc sulphate, zinc chloride and zinc gluconate are not spermicidal. This is probably due to the acetate in zinc acetate which may reduce oxygen utilization by the sperm[91]. Zinc acetate is used as an astringent at low concentration and as an irritant at high concentration. It is important to note that it shows spermicidal activity at a concentration of 1% which is about five times that used in topical formulations. The plasma concentration of zinc decreases rapidly in pregnancy and in women taking birth control pills. Therefore, the high concentration of zinc acetate in spermicidal formulations may in fact, be helpful in replenishing the zinc loss in women. However, this aspect is yet to be thoroughly investigated.

Aloe barbedensis (lyophilized, 7.5% and 10%) has been reported to be spermicidal due to the presence of microelements that are toxic to the sperm tail[91]. Tetrahedral metallocene complexes containing vanadium have recently shown to possess potent spermicidal activity. Among all the oxovanadium derivatives, the bis-phenthroline complex has shown the most potent spermicidal activity[92-94]. Sialic acid binds to certain receptors on the sperm membrane which results in decreased ATP metabolism and leads to reduced sperm motility[95]. An increase in sperm motility occurs after exposure of sperms to D-galactose[96,97]. Similarly, a specific oligosaccharide (glycoprotein-3) has been reported in sperm cell zona pellucida system[98]. Recognition of these specific sites on sperm membrane can provide a safe means of blocking sperm-oocyte fusion.

COMBINATION FORMULATIONS OF CONTACT SPERMICIDES

As is evident from the preceding sections, clinical use of many contact spermicides is hampered because of the risk of their systemic or local adverse effect. Therefore, a combination of two or more spermicides acting through different mechanisms may reduce the dose of contact spermicides, thereby minimizing the potential for adverse effects.

N-9 and EDTA act on the sperm by different mechanisms. In combination, EDTA reduces the loading dose of N-9 in the formulation. A combination of N-9 (100 mg/ml) and EDTA (0.01%) in carbopol 934P (0.01%) has been reported to exhibit total spermicidal action on human sperm[50]. Similarly, a combination of N-9 and propranolol also exhibits an additive spermicidal action[15].

Azadirachtin[99-101], *Sapindus mucorosii* and quinine hydrochloride are potent spermicidal agents. A formulation containing azadirachtin (0.39%), saponin from *Sapindus mucorosii* (0.015%) and quinine hydrochloride (0.0012%) has been reported to possess synergistic spermicidal action[102-103].

Gramicidin in combination with EDTA (0.1%) exhibits total spermicidal action at a concentration of 10 ng/ml as against 4 μg/ml when it is present alone or when combined with sodium edetate[51].

CONCLUSIONS

Contact spermicides have many physiological advantages over other methods of contraception. They also have a high acceptability index. To be a clinically effective contraceptive, a spermicide should ideally produce total immotility immediately on contact with sperm and the immobilization should be irreversible. It should not adversely affect the developing embryo. Although, many spermicides discussed here fulfill these criteria but their safety profiles have either not been evaluated or are not worthy enough to permit their clinical use. Surfactants possess good spermicidal activity but are irritating to genital mucosa. Propranolol, quinidine, mexiletine are systemically absorbed in significant concentration. Therefore, agents that specifically target the sperm may offer a novel means of male contraception[104]. However, there is a need to develop contact spermicides with better safety profile and to systematically evaluate the toxicological profile of existing contact spermicides. Additionally, the sperm functions should be evaluated more stringently after their treatment with contact spermicides as recommended by WHO manual[105].

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