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Does the intrauterine device carry the risk of immunity to sperm?

B. VURAL (1), F. VURAL (1), A. ÇORAKÇI (1), S. TÜRKOĞLU (2) and A. ERK (1)

(1) Department of Obstetrics and Gynecology, School of Medicine, Kocaeli University, Kocaeli, Turkey
(2) Department of Microbiology, School of Medicine, Istanbul University, Istanbul, Turkey

Abstract

Intrauterine devices (IUDs) are the second most commonly used contraceptive method in the world. A number of mechanisms have been proposed by which IUDs could interfere with reproductive processes. In this study, the relationship between intrauterine devices and the risk of antisperm antibody (ASA) production in the absence of prior sensitization was investigated. Sixty-two IUD users (group 1) and 42 women with no contraceptive use as a control group (group 2) were included in the study. Six months after the IUD insertion, 4 women in group 1 and 2 women in group 2 with lower genital tract infections were excluded from the study. The sera of the remaining 58 women in group 1 and 40 women in group 2 were evaluated again for the presence of ASA. Twelve patients (20.7%) in group 1 and 12 patients (30.0%) in group 2 had ASA positivity. When we compared the ASA levels in the IUD group with those in the control group, there was no statistically significant difference ($p > 0.05$). In summary, our data proved that copper-containing intrauterine devices in the absence of prior sensitization do not significantly affect immunity to sperm in sera of women.

Introduction

The experimental basis of immunity to sperm was first documented to cause induced infertility when Rümke and Hellinger [1] found that a significant number of men with infertility manifested an autoimmunity to spermatozoa. Subsequently, Franklin and Dukes [1] also demonstrated sperm agglutinins in the sera of women whose failure to conceive was otherwise unexplained. Sperm antibodies are a relative rather than absolute cause of infertility. Low levels of circulating antisperm antibodies (ASA) are

commonly detected in sera of fertile women [1]. Nineteen per cent of sera from pregnant women and 40% of sera from fertile women have these antibodies [2]. Sperm-specific antigens and their antifertility effects are also under investigation as the basis for immunological regulation of fertility through contraceptive immunization [3,4].

Although a sexually active female is exposed to a great number of potential antigens in the form of spermatozoa, the female immune system cannot usually be activated in this manner. Many factors are involved, such as the irritation of genital system mucosa which has an epithelial barrier effect on the peritoneum or the gastrointestinal mucosa, will induce ASA production in women [1,5].

Intrauterine devices (IUDs) are the second most commonly used contraceptive method in the world, and the most common method in Turkey [6]. Following widespread introduction of intrauterine devices in the 1960s, experimental studies have addressed the mode of action in a variety of species. Based on such observations, a number of mechanisms were proposed by which IUDs could interfere with the reproductive process and alter the human endometrium [7]. No study, however, shows the relationship between antisperm antibody production and intrauterine devices. This study was planned to investigate the relationship between copper IUDs and the risk of immunity to sperm.

Materials and methods

Study design

This study was performed on women who came to the Gynecology and Obstetrics Department of Kocaeli University School of Medicine, Kocaeli, Turkey, for family planning. After counselling and information about family planning were given, patients were selected according to the exclusion criteria cited below:

1. Women with menstrual irregularities, genital tract infection, suspicion of pregnancy, severe pelvic pain, history of ectopic pregnancy, uterine anomalies and fibroids, coagulation disorders, suspicion of malignancy, severe anemia and risk of sexually transmitted disease were excluded from the IUD program [8].

2. The presence of a history of gynecologic disease, autoimmune disorders, abdomino-pelvic surgery, infertility problems and sera positive for antisperm antibody were also exclusion criteria.

Subsequently 62 appropriate women were included in the study (group 1) and a copper T380A IUD was inserted appropriately. Forty-two similar women with appropriate study inclusion criteria, who decided not to use an IUD or any other contraceptive method, were taken as a control group (group 2). In both the study and control groups, none of the patients had a previous history of IUD use.

Six months later, women in both groups were evaluated again and detailed physical examinations and laboratory studies for genital tract infections were performed. Four women were excluded (1 with *Candida albicans*, 1 with *Trichomonas vaginalis*, 2 with bacterial vaginosis) from group 1 and 2 women (1 with *Trichomonas vaginalis* and 1 with *Candida albicans*) from group 2. The sera of the remaining 58 women in group 1 and 40 women in group 2 were evaluated again for the presence of antisperm antibodies.

Laboratory evaluation

Patients were evaluated for lower genital tract infection and antisperm antibodies twice, at the beginning and at the end of the study.

1. The diagnosis of *Trichomonas vaginalis* and candidial vaginitis were based on: symptoms, character of vaginal discharge, vaginal pH, and the presence of trichomonas in saline solution or hyphae and/or spores in potassium hydroxide preparations. Clue cell positivity on saline wet mount preparations was accepted as a diagnostic sign for the bacterial vaginosis. Patients were considered to have chlamydial cervicitis when a cervical swab specimen was reactive in an enzyme-linked immunoabsorbent assay (ELISA) (Clearview, Chlamydia MF, Cat. No. 2629A, Unipath Ltd, England) for *Chlamydia trachomatis* antigen, when more than 10 white blood cells per high power field were found in saline solution preparations of vaginal discharge. Gram staining was also performed on samples from all women routinely.

2. The Spermatozoa Antibody ELISA (IBL, Cat. No. RE 52029, Hamburg, Germany) procedure was used to assess for antisperm antibody (IgG, A and M) in women's sera. At the end of the procedure, the difference in optical density between coated and uncoated wells was calculated for each standard and sample (cut-off = 150 mU/100 μl).

Statistical analysis

The χ^2 test was used to compare ASA positivity between group 1 and group 2.

Results

Antisperm antibody was tested for in 62 IUD users (group 1) and 42 control subjects (group 2). All the women were multigravid and aged between 20 and 35 years; the characteristics of the women in both groups were similar. The ELISA test was used to screen for antisperm antibodies. Since a significant number of women with lower genital tract infection have antisperm antibodies, six months later, 4 women in group

1 and 2 women in group 2 were excluded from the study. The sera were collected for ASA testing from the remaining 58 women in group 1 and 40 women in group 2. Twelve women in group 1 (20.7%) and 12 women in group 2 (30.0%) had ASA positivity. When we compared the ASA levels of the control group with those of the IUD group, there was no statistically significant difference ($p > 0.05$). The results of ASA testing for women in both groups are shown in Table 1.

Table 1. The results of the ELISA procedure for detection of antisperm antibody (ASA) in sera of IUD-inserted women

	*ASA levels with ELISA technique (mU/100 ul)**			
	ASA positivity			*ASA negativity*
	151–500	*>500*	*Total*	*0–150*
Group 1 ($n = 58$)	2	10	12 (20.7%)	46 (79.3%)
Group 2 ($n = 40$)	8	4	12 (30%)	28 (70%)

*Cut-off level = 150 mU/100 ul. The difference between group 1 and group 2 is not significant for ASA positivity ($p > 0.05$)

Discussion

Ever since the pioneering work of Landsteiner and Metchnikoff showing that injection of sperm can produce an antibody response in animals, sperm have been of great interest as target antigens for controlling fertility [3]. Immunologic processes, especially the activity of antibodies against sperm, have been implicated as a cause of infertility [1]. Antisperm antibody production processes have also been the basis for some contraceptive vaccine investigations.

ASA may be of different immunoglobulin classes that interact with their complement in different ways, and their ability to alter sperm function may vary. ASA are also directed against several different antigens and have different effects on sperm functions [2]. The mechanisms for antisperm-antibody-mediated dysfunction are most likely to be via a decrease in sperm motility through the cervical mucus and upper reproductive tract or via an impairment of the processes that lead to oocyte fertilization [1,5,9].

Although women are regularly inoculated intravaginally with spermatozoa during coitus, this event is not usually associated with the development of antibodies. Immunoinhibitory substances have been detected and partially isolated in seminal plasma. However, the relationship between the presence or absence of immuno-

suppressive activity of seminal fluid and ASA production is intriguing [2]. If the semen, gastrointestinal or genital mucosa and peritoneum are not changed pathologically, the female immune system cannot usually be activated. The literature has suggested that, after a breach in the epithelial mucosal barrier of the female genital tract, sperm antigens may gain access to subepithelial B lymphocytes that are committed to the production of specific secretory IgA [1,5]. In the endometrial stroma, occasionally IgA and its secretory component was found in endometrial glands, especially during the secretory phase of the endometrium [10]. However, it is difficult to diagnose clinically relevant immunity to sperm in women, due to our current inability to sample adequately the secretions of the uterus and fallopian tubes. In addition, immunoglobulin secretions within each of the reproductive compartments (cervix, uterus, fallopian tubes) are under hormonal control and exhibit different mechanisms for the regulation of antibody transport [2].

The mechanisms by which IUDs effect contraception have not been defined precisely. But, a number of mechanisms have been proposed by which IUDs could interfere with the reproductive process and cause alterations in the human endometrium [7,11]. The contraceptive action of all IUDs is mainly in the uterine cavity. It is currently believed that the major mechanism of action for IUDs is the production of an intrauterine environment that is spermicidal. A sterile inflammatory response of the uterus to an IUD leads to lysosomal activation and tissue injury which is of a minor degree but sufficient to be spermicidal. The copper IUD releases free copper and copper salts, which both have a biochemical and morphological impact on the endometrium. Copper has many specific actions, including the enhancement of prostaglandin production and the inhibition of various endometrial enzymes. It may be that the overall inflammatory response is intensified. Following the removal of an IUD, the normal intrauterine environment and fertility are rapidly restored [12]. However, there is no literature on intrauterine devices and antisperm antibody production.

Although the mechanism underlying antisperm antibody production is unknown, it has been proposed that it arises, among other ways, as a consequence of local inflammation. Thus, genital tract infections might serve as non-specific immunopotentiators that lead to the production of antisperm antibodies [13,14]. Therefore, in this study, we excluded patients who had a lower genital tract infection or a history of genital tract infections. The local immune response could result in production of specific secretory IgA against sperm antigens. More significant exposure to sperm antigens at the systemic level would result in a systemic response to sperm which includes IgG [1,5,13]. Since there is no clinical method to assess the uterine environment for local antisperm antibody production [2,15], we could only determine ASA levels from sera of the patients. There was no statistically significant difference in ASA production between group 1 and group 2.

In summary, our data prove that intrauterine devices, in the absence of prior sensitization, do not significantly affect immunity to sperm. However, the role of the uterine environment in local antisperm antibody production provides challenges for ongoing research.

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Resumé

Les dispositifs intra-utérins viennent en second parmi les méthodes de contraception les plus utilisées dans le monde. Plusieurs mécanismes ont été proposés, selon lesquels ces DIU (dispositifs intra-utérins) interfèrent sur le processus de reproduction. On a étudié ici la relation entre les dispositifs intra-utérins et le risque de production d'anticorps antisperme (ASA) en l'absence d'une sensibilisation préalable. Soixante-deux utilisatrices de DIU (groupe 1) et un groupe témoin de 42 femmes n'ayant pas recours à la contraception (groupe 2) ont participé à l'étude. Six mois après l'insertion des DIU, 4 femmes du groupe 1 et 2 du groupe 2 ont été éliminées de l'étude à cause d'infection vaginale. Dans le sérum des femmes restantes (58 du groupe 1 et 40 du groupe 2), on a de nouveau recherché la présence d'ASA: les résultats ont été positifs chez 12 patientes du groupe 1 (20,7%) et 12 du groupe 2 (30%). La comparaison des résultats obtenus concernant les niveaux d'ASA des utilisatrices de DIU et du groupe témoin n'a pas révélé de différence statistiquement significative ($p > 0{,}05$). En résume, nos données suggèrent qu'en l'absence d'une sensibilisation préalable, les dispositifs intra-utérins contenant du cuivre n'ont pas d'effet significatif vis-à-vis du sperme dans le sérum des femmes.

Resumen

Los dispositivos intrauterinos (DIU) son, en orden de frecuencia, el segundo método anticonceptivo de mayor uso en el mundo. Se propusieron varios mecanismos según los cuales los DIU podrían obstaculizar el proceso reproductivo. En este estudio se examinó la relación entre los DIU y el riesgo de producción de anticuerpos antiespermáticos (ASA) en ausencia de una sensibilización anterior. Se incluyó en el estudio a sesenta y dos usuarias de DIU (grupo 1) y 42 mujeres sin uso de anticonceptivos como grupo de control (grupo 2). Seis meses después de la colocación del DIU, 4 mujeres del grupo 1 y 2 mujeres del grupo 2 con infecciones del tracto genital inferior fueron excluidas del estudio. El suero de las restantes 58 mujeres del grupo 1 y de 40 mujeres del grupo 2 fue evaluado nuevamente para determinar la presencia de ASA. Doce pacientes (20,7%) del grupo 1 y 12 pacientes (30,0%) del grupo 2 presentaron un resultado ASA positivo. Cuando se compararon los resultados de los niveles ASA del grupo DIU con el grupo de control, no se observó una diferencia estadísticamente significativa ($p > 0,05$). En resumen, nuestros datos señalaron que los dispositivos intrauterinos que contienen cobre, en ausencia de sensibilización anterior, no afectan significativamente la inmunidad al esperma en el suero de mujeres.