

EFFECT OF CHEMICAL WARFARE AGENTS ON FERTILITY

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ABSTRACT

A questionnaire-based study of infertility in Iran was carried out on two groups of people: those exposed to chemical warfare agents and those with no exposure. The prevalence of infertility (no conception after a 1-year attempt) was found to be approximately 16.2% in the group exposed to chemical warfare agents and 15.1% in the normal population. These findings suggest that there was no significant increase in the prevalence of infertility after single exposures to chemical warfare agents.

Key words: Chemical Warfare Agents, Infertility, Conception, Iran

INTRODUCTION

Chemical Warfare Agents (CWAs) were used in the Iraq-Iran war (United Nations document S/16433, 1986). Sulfur mustard (SM or agent HD), bis(2-chloroethyl)sulfide (505-60-2) is a lipophilic alkylating agent and was the predominant CWA used. Previous studies implicated alkylating agents as a cause of infertility (Chapman et al., 1981; Charak et al., 1990; Dhabar et al., 1993; Irvine, 1998). Some reports have shown that occupational exposure to antineoplastic drugs with an alkylating nature, which can damage DNA, can cause mutagenic, teratogenic, and carcinogenic effects, and also can increase reproductive risks, such as spontaneous abortion and congenital malformations (Selevan et al., 1985; Hemminki et al., 1985; McDonald et al., 1988; Taskinen, 1990; Stucker et al., 1990; Skov et al., 1992). The effects of these drugs on the gonads appear to be dose-related. However, the upper limit of the safe dosage has not been clearly established. As a result of the possible long-term effects on fertility that might result from exposure to SM during the Iraq-Iran war, we examined a group of people who were exposed.

There are no case-control studies regarding the effect of mustard gas exposure on fertility. Based on the similarity of SM with these alkylating drugs, we investigated the possibility that a single exposure to mustard gas could affect the fertility in those who had been exposed during the Iraq-Iran War. Most patients exposed to CWAs present a history of single exposure to mustard gas, but the concentration and duration of inhalation of mustard varied. Since we were examining the effects of CWAs and sorting through the records of those who had been exposed, we included those with single exposures to either

cyanide (HCN) or nerve agents (Abbas, 2003). A case-control study was conducted to elucidate any relationship between infertility and CWA exposure.

METHODS AND MATERIALS

In 1999, a case-control study was done in the Isfahan province of Iran to compare the infertility rate in a group of chemical warfare victims with that in a non-exposed control group. Infertility was clinically defined as the failure to conceive after 12 months of unprotected intercourse.

Case Study Group

Medical records of 2500 male patients with a history of chemical exposure were examined. Seven hundred twenty-four (724) patients were included in the study. The mean age of men in the case study group was 35 ± 4.2 years. This case study group was further divided into three groups, based on the particular agent to which the patients had been exposed.

Inclusion Criteria

1) Documentation of chemical exposure by military health services at the time of exposure. Exposure in this study was defined as a single, high-dose exposure to a chemical agent that causes transient or permanent disability in exposed people.

2) Medical records documented the type of warfare agents used or the combinations suspected and documented that the patient received medical care for chemical exposure. According to their records, all injured victims were transferred to local military hospitals, where, based on signs and symptoms (lacrimation, dyspnea, cough, skin blisters, erythema, or pruritis) and through the use of special kits, the types of chemical agents were determined (Abbas, 2003). Nerve agent exposure was suspected if the injured case presented with myosis and the symptoms were controlled by atropine. HD exposure was suspected if the injured cases presented with blisters and had continued respiratory symptoms. The physicians treated the patients using standard protocols determined by military health services.*

3) Criteria for women included in the case group. Wives of those included in the case study group were asked about their reproductive history in order to document infertility after their husbands returned from the hospital. All women that participated in our study were ages 42 or under, had never used oral contraceptives or intrauterine contraceptive devices, were not surgically sterilized, and were never exposed to chemical agents.

* Patients with signs and symptoms compatible with nerve agent exposure were treated with atropine, diazepam, and oxime; those who presented with blisters on their skin were treated with supportive care and sodium thiosulfate.

Exclusion Criteria

1) Infertility before exposure, as determined from the patient's history.

2) Associated chronic diseases, other than from chemical exposure, as determined from patient history and medical records. Patients with a history of chronic diseases that may cause loss of sexual dysfunction, such as diabetes, hypertension, heart disease, vascular problems, multiple sclerosis, and spinal cord injuries, were excluded.

Categories of Patients

The patients were classified into three groups based on the type of chemical exposure (sulfur mustard, nerve agents, or cyanide) based on medical documents. When the type of exposure could not be determined, or there was suspicion that mixtures of agents were used, the exposure was classified as unknown. Among the case study group, the type of agent was determined in only 555 cases; other cases were omitted from the study. All patients had a specific disability, determined by consulting an expert team and using well-designed criteria (Khateri et al., 2001). Based on a disability index, they were classified as mild, moderate, or severe.

Control Group

The control group was selected from a list of couples who visited pre-marriage counseling centers. Before marriage, all couples were referred for thalassemia screening (Ghanei et al., 1997). The mean age of men in the control group was 28.7 ± 4.52 years. A sample of 1000 married women (or every fifth woman from the list of couples) ages 18–45 years were requested to answer a questionnaire dealing with general medical, menstrual, reproductive, and contraceptive histories. Of the 1000 women, only 820 answered all the questions on the form and were included in the study based on the above-mentioned inclusion criteria (aged 42 or under, never used oral contraceptives or intrauterine contraceptive devices, not surgically sterilized, and never exposed to chemical agents). Only 10 cases in the control group refused cooperation with our project; thus, there were 810 cases in the control group. The fertility status of each participating woman was defined in this control group.

The only difference between the control group and the study group was the documented exposure to a chemical warfare agent. The participants in the control group had not been exposed to any chemical warfare agents. Both groups were selected from the same city and were exposed to similar conditions. The veterans were mostly volunteers rather than specialized military people.

Data Collection

A standard infertility questionnaire design, based on WHO guidelines, was used in this study (World Health Organization, 2001). Questions regarding exposure to chemical

warfare agents and disability were added for the case group. The translations of the additional questions are shown in figure 1 and figure 2.

This part should be filled only based on recorded documents (which are with the patient):

89) Date of hospitalization?

90) Name of the center?

a. Was it in a field?

b. Was it in a city?

91) Reason for referral?

92) Are there any recorded symptoms? Go to the following table please:

Sign or Symptoms	Yes	No	Not Mentioned	Related Orders
Erythema				
Blister				
Scaling				
Tearing eye				
Itching				
Conjunctivitis				
Blurred vision				
Myosis				
Cough				
Dyspnea				
History of post exposure seizure				
Sialorrhoea				
Others				

Note: In orders, some information is of great importance: dressing blisters, atropine usage, calamine ointment usage, silver sulfadiazine usage on blisters, permanganate 1/10000 bath, injection of obidoxime.

Figure 1. Additional questions for the case group regarding exposure to chemical warfare agents

Conditions at Time of Alleged Incident

- 10) How many times were you exposed?
- 11) Date:
- 12) Time:
- 13) Place:
- 14) How did you come to be there at the time?
 - a. Soldier
 - b. Voluntary soldier
 - c. Civilian
- 15) Where were you when the attack occurred?
 - a. Open air
 - b. Under cover
- 16) Did you have protection of any sort?
- 17) Did you do anything to protect yourself?
- 18) Who were you with?
- 19) What was the delivery method of the attack?
 - a. Bombs
 - b. Spray
 - c. Other
- 20) Did you receive any treatment?
 - a. What?
 - b. When?
 - c. Where?
 - d. How long?
 - e. Did you recover immediately?
- 21) Was there any odor?
- 22) Did you see any others affected or killed? How many? How many were not affected?

Figure 2. Additional questions for the case study group regarding conditions at the time of alleged incident

Statistical analysis was done with SPSS for windows. The significance of difference was assessed by X2 test for categorical variables. P value less than 0.05 was considered a significant result.

RESULTS

The infertility rate was determined to be 15.1% among control group and 16.2% overall among the case study group ($p=0.8$). The infertility rates in the case study group and in the control group are shown in table 1, along with the infertility rates between the three different agent-exposed groups in the case study group. There was no significant difference between the infertility rates from the three different agent groups, cyanide, SM and nerve agent. In table 2, infertility within the case study group with single exposure and those with two or more (multiple) exposures is shown. In two cases, the medical records were insufficient to make a decision and so were omitted from table 2. Data shown in table 3 are related to infertility within the case study group with different levels of disability; the limited number of cases with severe disability is presented in this table for better understanding of the total outcome in patients exposed to CWA.

Table 1. Infertility rates in the case study and control groups

Case Study Group	CWA Exposure*	Infertility Rate (percent)
363	SM	17.1
96	HCN	13.5
96	Nerve agent (tabun, sarin, or soman)	13.5
Control Group	CWA Exposure	Infertility Rate (percent)
810	None	15.1

* CWA exposure: one-time exposure.

Table 2. Infertility within case group with single and multiple exposures

	Single Exposure	Multiple Exposures	Total
Infertile cases	89	29	118
Fertile cases	466	138	604
Total	555	167	722
Infertility (percent)	16.0	17.4	16.3

Table 3. Infertility within case study group and with different disability

Disability	Mild	Moderate	Severe*	Total
Infertile cases	108	8	2	118
Fertile cases	557	41	8	606
Total	665	49	10	724
Infertility (percent)	16.2	16.3	20	16.3

* Severe cases are presented to allow a better understanding of the total outcome of patients exposed to CWAs; however, due to the limited number of cases, these statistical values were not included in the study or factored into the total percent of infertile cases.

DISCUSSION

The World Health Organization estimates that 8% of couples or 50 to 80 million people worldwide experience some form of infertility (World Health Organization, 1987). In industrialized nations, approximately 10–15% of couples experience either primary or secondary infertility. The European Studies of Infertility and Subfecundity reports that 16% of the population has a waiting time of more than 12 months to become pregnant (Juul et al., 1999).

Our study showed that in our non-exposed control group, infertility with 15.1% prevalence is the same as other countries. This study also showed that exposure to CWA does not affect infertility; the infertility rate we observed was 16.2% for all exposures (mild and moderate) or 116 infertile cases out of total 714 cases (table 3). This is not significantly different from the non-exposed control group's infertility rate. Although the infertility rate was 20% in severe cases, this represents only a limited number of cases and may include changes in sexual habits due to severe pulmonary disease. These cases were not included in the 16.2% infertility rate.

A study on chemical victims in Iran demonstrated that exposure to SM results in very low androgen levels and hypo-responsiveness to gonadotropin releasing hormone (GnRH) in the first five weeks and is normal by the twelfth week after injury. The researchers suggested that side effects of mustard on sperm cells persist and may cause defective spermatogenesis years after exposure (Azizi et al., 1995). However, further research on spermatogenesis by that group was not published. Although we did not assess gonadal hormones, sperm count, or spermatogenesis, based on our case study and the lack of influence of exposure on infertility rate, we believe that gonadal hormones in that study remained unchanged after 12 weeks and did not cause infertility.

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