Pregnancy Outcomes of Wives of Chemical and Non-Chemical Weapons Exposed Veterans in Ahvaz, Iran: A Retrospective Cohort Study

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Abbreviations:
FMVA: Foundation of Martyrs and Veterans Affairs
GI: gastrointestinal
GU: genitourinary
HD: Sulfur Mustard

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Abstract

Background: Sulphur mustard (HD) is a lipophilic caustic alkylating vesicant (blister agent) that has mutagenic and carcinogenic effects. Among the studied perturbations are long-term genitourinary (GU) and fertility effects. Approximately 50,000 Iranian soldiers and civilians were exposed to HD during the Iraq-Iran war (1980-1989). This study questioned the wives of Iraq-Iran war veterans to determine the effects of male HD-exposure on pregnancy complications, adverse pregnancy outcomes, and secondary infertility.

Methods: A retrospective, survey-based cohort study was conducted of wives of Iranian military veterans that survived HD-associated injuries while serving in Ahvaz, Iran during the Iraq-Iran war (1980-1989), as compared to non-exposed veterans serving concomitantly. Patients were identified from a database of injured veterans maintained by the Foundation of Martyrs and Veterans Affairs (Iran) via a systematic random sampling method utilizing a random number table. Using a validated questionnaire, collected data included: demographics; type and severity of chemical injury; spouse's obstetric history (pregnancy number, duration, complications, and outcomes before and after spouse's chemical injury); and secondary infertility.

Results: An increase in spontaneous abortion ($P = .03$), congenital anomalies ($P < .0001$), and secondary infertility ($P = .003$) were observed. These findings were greatest amongst those with HD injuries affecting >50% body surface area. No difference in stillbirth, premature birth, or low birth weight was observed.

Conclusion: Exposure to HD in combat may have long-lasting fertility effects on soldiers and their spouses, including spontaneous abortion, congenital anomalies, and secondary infertility. Further investigation is needed into the long-term effects of HD exposure as well as methods to better protect soldiers.

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Introduction

Sulphur mustard (HD), synthesized in 1822 by Despretz, is a lipophilic caustic alkylating vesicant (blister agent) that interferes with DNA integrity, cell-repair mechanisms, and replication.[1-5] As such, it has mutagenic and carcinogenic effects.[3,6] It is a colorless, oily, and odorless liquid, hardly soluble in water but easily dissolved in oils and alcohol.[2] It was first used in World War I as an offensive weapon by the Germans during an attack against the British at Ypres, Belgium in July 1917.[7] Since then, mustards have been used in several other conflicts despite the Geneva accords.

Although more toxic and effective chemical warfare agents are available, HD remains useful because it is highly toxic, difficult to treat, versatile, persistent, cheap, easy to produce industrially, and difficult to protect against. Moreover, HD is toxic when deployed as liquid, droplets, vapor, or as an aerosolized cloud.[7]

It causes severe, delayed burns to the eyes, skin, and respiratory tract. It damages cells within minutes of contact, however, the onset of pain and other health effects is delayed until hours after exposure.[8] Large exposures may cause respiratory distress, convulsions, and death.[7,8] Its DNA cross-linking causes hematologic cell toxicity.[8] Finally, HD causes cholinergic toxicity, marked by excessive saliva, tears, and urine; gastrointestinal (GI) distress;

and miosis.[7,8] Apart from its acute effects, HD induces a wide-range of long-term pathological effects on the skin, eyes, respiratory tract, immune system, and in some cases on the GI, cardiovascular, nervous, and genitourinary (GU) systems.[9] Among the GU effects are sexual dysfunction, infertility, pregnancy complication, spontaneous abortion, or congenital malformation.[7] While short-term GU effects have been described, the long-term GU sequelae of HD exposure remain unclear.

Approximately 50,000 Iranian soldiers and civilians were exposed to HD during the Iraq-Iran war (1980-1988).[1,10] This project aimed to address the following research question: Among the wives of Iranian veterans of the Iraq-Iran war that served and reside in Ahvaz (Population), does male HD-exposure (Intervention) compared to no exposure (Comparison) increase rates of pregnancy complications, adverse pregnancy outcome, or secondary infertility (Outcomes)?

Methods

Study Design and Setting

A retrospective, survey-based cohort study was conducted. All study parts were reviewed according to the *Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.*[11] The study was approved by the Investigative Review Board at the Foundation of Martyrs and Veterans Affairs (FMVA; Iran; #IR.ISAAR.REC.1397.005). Patients were identified from the FMVA database of injured veterans through a systematic random sampling using a random number table. Study participation was optional. Written consent was required and included both study participation and publication of de-identified aggregate results. Surveys were conducted in person. No incentives were offered (eg, monetary, prizes, or non-monetary incentives) for study participation. Survey items were not randomized. Only completed surveys were analyzed. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Location

Ahvaz (population 1,300,000) is the capital of Khuzestan Province in southwest Iran. In 2011, Ahvaz accounted for approximately 34% of Kuzestan's urban population and served as an integral support center during the Iran-Iraq war.[12] Iranian soldiers and civilians in Ahvaz were the subject of Iraqi chemical weapons attacks. Of the 3,400 surviving chemical war veterans in Khuzestan, 1,100 live in Ahvaz.[13]

Participants

The study population consisted of the wives of Iranian military veterans who survived HD injuries incurred during battles in Ahvaz during the Iran-Iraq war. Potential participants were identified through FMVA records; FMVA is an Iranian foundation funded by the national government that supports and maintains records on the etiology and nature of injuries and disabilities affecting combat veterans. Records were screened according to inclusion and exclusion criteria. Control participants included the wives of non-HD-exposed veterans serving in Ahvaz concomitantly. Potential participants were contacted by telephone. For persons meeting inclusion criteria who were agreeable to participate, researches travelled to their homes to administer the survey in person.

The inclusion criteria were: (1) no exposure of veteran to chemical weapon other than HD; (2) wife's pregnancy occurred only after spouse's HD exposure; (3) maternal age at time of pregnancy between 18-40 years; and (4) resident of Ahvaz during pregnancy and study period. Exclusion criteria were: (1) high-risk pregnancy for medical reasons prior to HD exposure (eg, first pregnancy at age >35 years, multiple gestations, chromosomal abnormalities, any miscarriage, preeclampsia, eclampsia, HELLP syndrome, pre-term labor, delivery complications, fetal anomaly, or stillbirth); (2) medically high-risk pregnancy during study period (same definition); (3) high-risk occupation during pregnancy (eg, physically strenuous or toxin or radiation exposure); (4) veteran had significant combat injuries apart from HD exposure; (5) emigration from Ahvaz; and (6) divorce of veteran and spouse.

Sulfur Mustard Exposure

Exposure to HD was defined as any person having any physical contact with HD and experiencing medical symptoms, with the case being registered with FMVA. Exposure could have occurred either in a closed or open space. Injury was quantified in terms of total body surface area affected.

Research Instrument

The data collection tool was developed by the research team and contained questions on demographics (age, occupation, and education level); veteran's chemical injury (type and severity); spouse's obstetric history (pregnancy number, duration, complications, and outcomes before and after spouse's chemical injury); and secondary infertility. Pregnancy complications included preeclampsia, eclampsia, HELLP syndrome, and pre-term labor. Adverse pregnancy outcomes were defined as miscarriage, stillbirth, pre-term delivery, low birth weight, and fetal anomaly.

Qualitative content was validated through review by 10 faculty members and experts in reproductive health and questionnaire development. Face validity was validated through tool review by 15 veteran's wives of varying occupations and education levels. Content validity was assessed with two content validity ratios of 10 panels equal to 0.75 and content validity index equal to 0.87. The test-retest method was used to measure consistency and determine the external reliability. To achieve this, questionnaires were distributed to 20 HD-exposed veteran's wives, completed and collected at two stages with a 14-day interval. The observed correlation coefficient was 0.78. The internal validity of the questionnaire as determined by the Cronbach's alpha coefficient was 0.89

Sample Size

There were 1,100 chemical war veterans living in Ahvaz. Sample size analysis was based upon a pilot of 30 veterans living in Ahvaz. Among them, 10 veterans were in the case group and 20 veterans were in the control group. Type I error was 0.05 and Type II error was 0.10. The sample size in the case group was $n = 68$, and twice that in the control group (22-24). According to the probable sample size drop, 100 subjects were selected in the case group and 160 subjects were selected in the control group.

Data Analysis

All analyses were performed using IBM SPSS 23.0 (IBM Corp.; Armonk, New York USA) and GraphPad Prism 5 (GraphPad Software Inc.; La Jolla, California USA). The normality of study variables was assessed via One-Sample Kolmogorov-Smirnov test. Descriptive statistics were calculated for all variables. Categorical variables were compared using the Chi-Square. Univariate and multivariate logistic regression were used to identify those factors exerting a statistically significant effect on the defined outcomes.

Variable	Sulfur Mustard (n = 70)	Control (n = 160)	P Value[a]
Age, Years, n (%)			
45-54	42 (60.0)	96 (60.0)	.999
55-64	22 (31.4)	50 (31.2)	
> 64	6 (8.6)	14 (8.8)	
Highest Education Level, n (%)			
Secondary School	38 (54.3)	84 (52.5)	.969
Undergraduate Degree	22 (31.4)	52 (32.5)	
Graduate Degree	10 (14.3)	24 (15.0)	
Employment Status, n (%)			
Home Maker	55 (78.6)	127 (79.4)	.89
Employed	15 (21.4)	33 (20.6)	
Child Number per Couple, mean	2.77	2.78	.825
Number of Couples per Child Number, n (%)			
1	9 (12.9)	21 (13.1)	
2	20 (28.6)	40 (25.0)	
3	19 (27.1)	53 (33.1)	
4	22 (31.4)	46 (28.8)	
Child Sex, Female, n (%)	125 (64)	197 (44)	<.001

Table 1. Participant Demographics
[a] Chi-square

Variable	Exposed n (%)	Control n (%)	Odds Ratio (Confidence Interval)	P Value[a]
Spontaneous Abortion, Yes	13 (18.6)	14 (18.8)	2.38 (1.05 - 5.37)	.03
Stillbirth, Yes	6 (8.6)	15 (9.4)	0.91 (0.34 - 2.44)	.85
Premature Birth, Yes	6 (8.6)	10 (6.2)	1.41 (0.49 - 4.03)	.52
Low Birth Weight, Yes	4 (5.7)	13 (8.1)	0.69 (0.22 - 2.18)	.52
Congenital Anomaly, Yes	15 (21.4)	4 (2.5)	10.64 (3.39 - 33.42)	<.0001
Secondary Infertility, Yes	16 (22.9)	14 (8.8)	3.09 (1.41 - 6.76)	.003

Table 2. Pregnancy Outcomes for the Wives of Soldiers Exposed to Sulfur Mustard as Compared to Controls
[a] Determined via binary logistic regression with backward method.

In the univariate model, each variable was entered in the model. In the multivariate model, backward elimination was utilized. Significance was determined as an alpha of 0.05. No interim analysis was planned or conducted.

Results

One-hundred subjects were included in this study. Thirty subjects were excluded and 70 were included in the final analysis. Demographics are presented in Table 1. The specificity of the HD-associated injury diagnosis in the FMVA records was 100%. No significant difference was found between the two groups in terms of age, education level, or occupation (Table 1). The results showed that the mean time between HD injury and pregnancy was four years in the case group. A total of 194 children (2.77 per study unit) were born in the HD group, whereas 444 (2.78 per study unit) were born in the control group (P = .825). Furthermore, number of children per study unit did not differ between groups (zero to four). The frequency of female children was significantly higher in the HD versus control group (64% versus 44%; P < .001). Secondary infertility was more than three-times higher in the HD group (22.9% versus 8.8%; P = .003). Similarly, the incidence of spontaneous abortion (18.6% versus 8.8%; P = .03) and congenital anomaly (21.5% versus 2.5%; P < .0001) were significantly higher in the HD group (Table 2). The incidence of stillbirth, premature delivery, and low birth weight did not differ significantly between groups.

When stratifying case subjects by severity of chemical injury (25%-49% versus >50%), only the incidence of spontaneous abortion was increased in the greater severity group (5.6% versus 32.4%; P = .01; Table 3). Analysis via multiple logistic regression testing of demographic and study variables was significant only for HD-exposure severity (P < .05).

Discussion

Blistering agents come in three types: HD, nitrogen mustard, and Lewisite (developed, but not used). Occasionally, phosgene oxime is included among blistering agents, although it is more properly termed a nettle agent (urticant). Approximately 50,000 Iranian soldiers and civilians were exposed to HD during the Iraq-Iran war (1980-1988).[1,10] Although the short-term toxicities are well-described, the long-term GU consequences remain unclear. Similar to prior reports, this study showed an increase in secondary

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Variable	% Body Surface Area Affected		Odds Ratio (Confidence Interval)	P Value[a]
	25%-49%	>50%		
Spontaneous Abortion, Yes	2 (5.6)	11 (32.4)	8.13 (1.65 - 40.14)	.01
Stillbirth, Yes	2 (5.6)	4 (11.8)	2.27 (0.39 - 13.27)	.36
Premature Birth, Yes	4 (11.1)	2 (5.9)	0.50 (0.85 - 2.93)	.44
Low Birth Weight, Yes	1 (2.8)	3 (8.8)	3.39 (0.34 - 34.27)	.30
Congenital Anomaly, Yes	4 (11.1)	11 (32.4)	3.83 (1.08 - 13.54)	.04
Secondary Infertility, Yes	2 (5.6)	14 (41.2)	11.90 (2.45 - 57.84)	.002

Table 3. Pregnancy Outcomes for the Wives of Soldiers Exposed to Sulfur Mustard Stratified According to Percent of Body Surface Area Affected

[a] Determined via binary logistic regression with backward method.

infertility, a finding seemingly driven by those with greater exposure (>50% body surface area).[9,14-16] This may, in part, be due to decreased sperm count and concentration,[3,15,17] increased azoospermia,[15] and possibly decreased sperm motility.[3] Long-term effects on sex hormones have been inconsistent, including luteinizing hormone (increased,[14,18] no change[3,4,15]), follicle-stimulating hormone (increased,[3,14,18] decreased,[15] no change[4]), testosterone (decreased,[18] no change[4,15,19]), and prolactin (no change[4]).

Despite this information, the long-term effects on pregnancy have not been well-characterized. The spontaneous abortion rate amongst the general population in Iran remains unclear. An increase in long-term spontaneous abortions was observed following paternal HD exposure, a finding seemingly driven by those with greater HD exposure (>50% body surface area; Table 3).[14,16]

No change in the long-term incidence of stillbirth, low birth weight, or premature birth was observed. The incidence of stillbirth was in keeping with prior studies in the Iranian general population (3.73 - 12.74 per 1,000 births),[20-22] as were the rates of low birth weight (incidence 3.35% - 4.86%; prevalence 11.8%)[22,23] and premature birth (incidence 1.5% - 5.1%; prevalence 9.2%).[24-26]

Congenital malformations in the control group were on par with those in studies of the general Iranian population (3.09 - 11.7 per 1,000 live births).[27-30] Conversely, the rate amongst the children born of an HD-exposed father was significantly increased. These findings corroborate those of other published studies.[14,31] Additionally, the discrepancy in baby gender between the groups raises the question of whether HD effects the Y chromosome to a greater extent than the X chromosome.

Lastly, the prevalence of secondary infertility in prior studies in the Iranian general population has been reported as 1.23% - 5.52%,[32-36] although the incidence remains unclear. The incidence for control patients in this study was 8.8%, whereas the incidence was significantly higher in the HD-exposed group.

Limitations

This study had limitations. The funding and logistical support was lacking to allow for analysis of sex hormones or sperm morphology or function. Additionally, only those veterans still residing in Ahvaz were eligible for inclusion and analysis. The ability to track those who had moved to other regions of the country or abroad was lacking.

Conclusions

Sulfur mustard exposure in combat may have long-lasting fertility effects on soldiers and their spouses, including spontaneous abortion, congenital anomalies, and secondary infertility. This is the first study to report long-term data on stillbirth, premature birth, or low birth weight for children born to an HD-exposed parent. Further investigation is needed into both the long-term effects of HD exposure and methods to protect soldiers.

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