Arch Iran Med. April 2020;23(4 Suppl 1):S16-S22

doi 10.34172/aim.2020.s4

http://www.aimjournal.ir

ARCHIVES OF IRANIAN MEDICINE

Review Article

Open Access

Impact of War on Fertility and Infertility

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Abstract

Background: War causes more death and disability than many major diseases. There are few studies in the context of the deleterious impact of war on fertility potential; therefore, in this study, we tried to review articles about the adverse effects of war on male/female fertility potential

Methods: In this study, a total of 183 articles related to the effects of war on fertility potential were examined by a systematic search using known international medical databases.

Results: Among these studies, there were limited studies on the effects of war on female infertility and most studies examined the effects of war on sperm parameters and male infertility. The physical and psychological trauma of war can increase the risk of infertility in men and women. Presence of reproductive system toxins in weapons, stressful periods of war and direct damage to the reproductive system can impair the fertility of men and women. The way war affects male fertility is not clear, but the higher degree of stress during wartime seems to play an important role. Using reproductive toxicants during the war also increases the risk of impairment in reproductive function in men. Some studies have shown the harmful effects of Sulfur mustard as a war chemical toxin especially on sperm quality and male infertility. Oxidative stress induced by free radicals is a major mechanism for the direct effects of Sulfur mustard on male infertility.

Conclusion: The study of past research suggests that exposure to war may be an independent risk factor for reproductive disorders and infertility in men. For female infertility, war leads to menstrual dysfunction.

Keywords: Chemical warfare, Free radicals, Infertility, Mustard gas, War-Related injuries

Cite this article as: Bolouki A, Zal F. Impact of war on fertility and infertility. Arch Iran Med. 2020;23(4 suppl 1):S16–S22. doi: 10.34172/aim.2020.s4.

Received: February 26, 2019, Accepted: October 12, 2019, ePublished: April 1, 2020

Introduction

Warfare can lead to death and disability more than any other malignant disease in societies. War destroys family and community frames and sometimes even destroys the intact cultural and identity foundations of a society. The socio-economic problems in war-torn countries are rising sharply, even sometimes affecting the economic affairs of other countries. Medical support and other human services are profoundly influenced by war, which undermines public health in the country.[1,2]

In recent years, several studies have examined the destructive effects of war on various aspects of reproductive disorders. One of the negative effects of war on the reproductive system has been its effects on fertility. However, there are restrictions on studying the consequences of war on fertility in war-torn countries. One of the biggest obstacles is collecting accurate epidemiological data about the pregnancy history of soldiers and inhabitants of war-torn zones. Besides, poor economic conditions and lack of funding in the war-torn countries are other problems for such studies. For this reason, most studies in this field are based on self-reported information and infertility registrations. Furthermore, most studies have focused on male fertility problems and few have been conducted on female fertility problems.

The precise mechanism of how warfare affects the fertility and reproductive systems is not entirely understood. Evidence suggests that war-related exposure, trauma and extremely toxic pollutants in weapons can severely affect men/women's fertility.[3-5] Therefore, given the devastating effects of war on the fertility of men and women and future generations, in this study, we attempted to review important studies published to date in this field.

Materials and Methods

In this study, we examined 183 articles related to the effects of war on male and female fertility. Systematic search was performed on international medical databases such as Medline, ISI, PubMed, and Scopus as well as Iranian medical databases such as SID, Irandoc and Iranmedex. Only articles published from 1960 to 2018 were reviewed in this study. The keyword used in the search was 'war' and the search terms used were 'infertility', 'female infertility', 'male infertility', 'menstrual cycle', 'menstrual period', 'menstrual irregularity', 'menstrual aberration', 'amenorrhea', 'semen parameters' and 'sperm quality', 'sex hormones' and 'reproductive systems'. Since fertility is mainly dependent on sperm quality in men

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and menstrual health in women, we also reviewed studies that investigated the effects of war on sperm parameters and menstrual health. Our main focus was to study the effects of war on the fertility of men and women. People who have been unsuccessful in pregnancy for more than one year are considered infertile. We reviewed studies involving indigenous populations and soldiers in war zones. Studies that included other severe reproductive disorders such as congenital malformation, miscarriage, fetal malformation, ectopic pregnancies, spontaneous abortion, and modification in sex ratio were excluded.

Results

In this systematic study, a total of 183 articles were investigated. Some of the studies on female and male infertility are presented in Table 1 and Table 2, respectively. In this study, we investigated the effects of sulfur mustard (SM), as one of the most common chemical warfare agents, on the male reproductive system, some of which are presented in Table 3. Our study is in accordance with the rules of the ethical review board of Shiraz University of medical sciences. This assessment covers the following key areas: deleterious effects of war on the menstruation cycle and fertility, stress and menstruation cycle irregularity, impact of war on men fertility, effect of war on environmental degradation as a factor associated with reproductive health and infertility, effect of SM on fertility, and the oxidative stress induced by SM.

Deleterious Effects of War on the Menstruation Cycle and Fertility in Woman

Evidence has indicated that menstrual dysfunction is very prevalent in the periods of long warfare. One study evaluated the effect of imprisonment of women in German camps during World War II on the health of menstruation and fertility. The study reported that women prisoners had severe short-term disorders in the menstrual system.[6] In another study, the acute and long-term effects of Hiroshima and Nagasaki atomic bombs on pregnancy and infertility in Japan were investigated. Yamazaki et al[31] found excessive fetal loss and infant mortality, but no change was shown in the fertility potential. Seigel evaluated the effect of war on fertility over a 16-year period from 1945 to 1961 among Japanese official family registration records, and no significant differences were found in the number of live births.[7] A more detailed study was published in 1972 confirming the results of prior studies. In this study, fertility was evaluated over 18 years, and it also included a calculation of radiation dose.[7]

Studies of the Desert Storm operation in Iraq in 1996

Table 1. Summary of Some Published Papers on the Effects of War on Women's Fertility

Reference	Population Under Study	Study Design	Results
Pasternak and Brooks[6]	World War II: Imprisoned women in German concentrations camp	Interview survey of Menstrual and reproductive histories of the women	Amenorrhea increased significantly in the imprisoned women. After liberation, 8.9% of the women resumed menstruation.
Blot and Sawada[7]	Surviving women exposed to the atomic bombs of Hiroshima and Nagasaki	Interview survey	Female fertility potential has not changed in surviving women exposed to high doses of atomic radiation.
Hannoun et al[8]	Lebanese war: Women exposed to war in 1996	Interview survey of Menstrual history	Women who remained in conflict zones showed 35% menstrual disorders and women who fled war zones showed a lower percentage of menstrual disorders.
Katon et al[9]	US: Male and Female veterans of operation enduring freedom/operation Iraqi freedom	Self-reported infertility	Lifetime history of infertility was 15.8% in women and 13.8% in men.

Table 2. Summary of Some Published Papers on the Effects of War on Men's Fertility

Reference	Population Under Study	Study Design	Results
Stellman et al[10]	Vietnam war: American soldiers who served during the Vietnam War	Male fertility questionnaire	There were no significant differences in conception problems in American Legionnaires.
Ishoy et al[11]	Danish veterans of the Gulf War	Interview survey with blood samples	No changes in sex hormones and fertility were observed among Danish veterans.
Sim[12]	Australia: male and female veterans in the Gulf War	Postal survey with clinic visit for a general health examination of infertility	Risk of conception difficulties was increased among male veterans.
Maconochie et al[13]	UK: male veterans of the Gulf War	Postal survey with clinical validation of reported infertility problems	Reported infertility was higher among UK male veterans.
Kelsall et al[14]	Australia: male veterans of the Gulf War	Self-administered postal questionnaire	Australian male veterans showed an increased rate of fertility problems.
Abu-Musa et al[15]	Lebanon: males exposed to war (1985–1989)	Retrospective review of patient records and clinical semen analysis	Sperm concentration was markedly reduced during war in comparison to post-war period.
Kobeissi et al[16]	Lebanon: males exposed to the long-term civil war (15 years)	Clinic-based, case-control study, using reproductive history and laboratory-based semen analysis	This long-term civil war impacted the male fertility.

Table 3. Toxic Effects of SM on Male Reproductive System

Study Model	Duration	Effects	References
SM victims	Several years	↓ Infertility (23.3%); ↓ Sperm quality (38.7%); ↑ Abortion (13.6%); ↑ Sexual dysfunction (9%); ↓ Libido (30%); ↑ Premature ejaculation (23.6%); ↑ FSH (57.6%); ↑ LH (66.3%)	Pour-Jafari and Moushtaghi[17]; Ketabchi[18]
SM victims	1st week after exposure	↓ Free serum testosterone; ↓ Dehydroepiandrosterone (DHES)	Azizi et al[19]
SM victims	5th week after exposure	↓ Free serum testosterone; ↓ Dehydroepiandrosterone (DHES)	Azizi et al[20]
SM victims	3rd and 5th week after exposure	↑ Serum FSH; ↑ Serum LH	Azizi et al[20]
SM victims	3 years after exposure	Y Free serum Testosterone; ↑ Testicular atrophy; Y Spermatogenesis; ↑ Sertoli cell only pattern	Azizi et al[20]; Safarinejad[21]; Amini and Hosseinpour[22]
SM victims	20 years after exposure	Normal LH, FSH and Testosterone	Amirzargar et al[23]
SM victims	3 months after exposure	↑ Oligozoospermia (33.3%)	Azizi et al[20]
SM victims	4 years after exposure	↑ Sperm counts (172 × 106)	Amirzargar et al[23]
SM victims	10 years after exposure	↑ Abnormal sperm (38%); ↑ Abnormal morphology of sperm (54%); ↓ Sperm motility (48%)	Shakeri et al[24]
SM victims	15 years after exposure	↑ Oligozoospermia (10%)	Ghanei et al[25]
SM victims	20 years after exposure	↓ Semen volume; ↓ Sperm counts; ↓ Sperm motility; ↓ Normal morphology of sperm	Amirzargar et al[23]; Pour-Jafari and Moushtaghi[26]; Safarinejad[27]
SM victims	20 years after exposure	↑ Sperm DNA damages	Safarinejad[27]
SM victims	8 years after exposure	↓ Libido (33.3%); ↑ Erectile dysfunction (9%); ↑ Premature ejaculation (23.6%)	Ketabchi[18]
SM victims	Few hours or few days after exposure	↑ Genital lesions; ↑ Hypopigmentation	Balali-Mood and Hefazi[28]
Male rats	10 days	↑ Abnormal sperm; Y Sperm counts; Y Sperm motility	Sasser et al[29]
Male rats	10 days	↑ Abnormal sperm; Y Sperm counts; Y Sperm motility; ↓ Free serum testosterone; ↓ Testis weight	Kooshesh et al[30]

indicated that menstrual irregularities during the war were very prevalent among American women soldiers. Indeed, these women soldiers had abnormal uterine bleeding,[32] such as long periods of menstruation and missed periods of menstruation.[33]

Using the data from a nationally representative survey conducted in 1996, Agadjanian and Prata examined the adverse effects of war on the timing of deliveries and war-related disorders in fertility potential in Angola.[34] They found that fertility was considerably reduced in the wartime period and subsequently increased in the postwar period, and these significant changes in fertility potential depended on the period of exposure to war and women's socioeconomic aspects. In another study, researchers indicated that Angolan women's fertility potential significantly decreased during the conflict peak and increased in the relatively peaceful period. These notable changes in women's fertility potential in the Angola conflict were stronger in regions more affected by war than those less affected.[35]

The Lebanon war is one of the wars considerably affecting women's menstruation and reproductive health. A study was conducted on menstruation health of women living in small towns and villages in southern Lebanon that were bombed in the date of April 11–27, 1996.[8] The results showed that short-term warfare can act as an extremely stressful condition and lead to severe menstrual problems.[8]

Women comprised approximately 7% of the US military in the Gulf War. Some results indicated high rates of women's problems such as abnormal Papanicolaou (Pap) smears, vaginal yeast infections, infections of bladder and breast and uterus cysts among female Gulf War veterans. One of the major studies investigating the reproductive health of female Gulf War veterans was the National Health Survey/Longitudinal Health Study. In this study, a sample of 30 000 veterans participated in 1995 and again in 2005 and 2012. Ectopic pregnancy and spontaneous abortion were increased among the women participating in this study.[9]

Unfortunately, to the best of our knowledge, there is no study examining the impact of the Iran-Iraq war on menstruation function and infertility rate among woman living in war-torn cities and villages in southern Iran.

Stress and Menstruation Cycle Irregularity

Many organs and hormones in the female body regulate menstrual cycles. The hypothalamic-pituitary-ovarian axis plays a vital role in regular menstruation in women.[4] Furthermore, regular menstrual cycles are very important in having a functional reproductive system. Studies show that factors such as stress, smoking, and malnutrition are associated with irregular menstruation and early menopause. Physiological stress has been shown to cause

menstrual perturbations.[36-38] In a study by Yao et al, the effects of occupational stress on menstruation and female sex hormones were examined. The authors showed that a higher stress degree significantly increases FSH and estrogen levels and reduces testosterone levels. They concluded that stress could lead to menses disorders. In addition, previous studies indicated that increased childhood adversity might result in adult fertility disorder; however, the accurate mechanism is unclear.[36] In another study, Jacobs et al examined how childhood adverse experiences can affect menstrual cycle indices and fertility problems. They concluded that the deleterious effects of childhood stress on fertility are the result of the impaired hypothalamic-pituitary-ovarian axis that suppresses fertility in response to less optimal reproductive conditions.[37] It can be concluded that stress has negative effects on menstrual cycle indices and menstrual disorders can eventually lead to fertility problems. It can be very clearly stated that wartimes is the most stressful period that people may encounter in any society. Therefore, it can be suggested that a high degree of physiological stress in the wartime period can cause menstrual cycle abnormalities and subsequently, reproductive problems and reduction of fertility among women.

Impact of War on Men's Fertility

Studies show that exposure to war increases the risk of fertility in men. Various reproductive toxicants are among the risk factors that increase the risk of infertility in men during war. War stresses, as well as direct damage to the reproductive system, are other important risk factors that increase infertility rates in men. Previous studies reported that stress has deleterious impacts on various parameters of semen quality such as semen concentration, morphology, and motility.[39-41]

The Joint Commission for the Investigation of the Atomic Bomb reported (1956) that sperm counts are reduced in those proximally exposed to atomic bombs. Besides, histological gonadal changes have markedly seen in fetal cases.[42]

In one study, DeStefano et al investigated semen characteristics among Vietnam War veterans.They found lower sperm concentration among Vietnam veterans, and rate of abnormalities in sperm morphology was also significantly increased among Vietnam War veterans.[41]

In 1991, a short war occurred in Slovenia, Zorn et al examined the effects of the stress associated with this war on men's fertility potential and sperm quality indicators.[43] The authors identified that sperm motility was significantly decreased, while sperm concentration and morphology remained unchanged. Moreover, in this study, a significant reduction of sex ratio at birth was observed. They concluded that acute psychological stress caused by a short war in Slovenia could lead to adverse changes in sperm motility and ultimately reduction in the observed sex ratio at birth.

The Lebanese civil war was one of the most destructive wars lasting for 15 years (1975–1990) with adverse effects on fertility potential in men. Many studies have shown that the Lebanese war has severely weakened the socio-economic and public health conditions in the country. The prolonged Lebanese war destroyed Lebanese infrastructure and severely damaged the environment, social services and medical care.[15] Besides, the inappropriate disposal of toxic waste and the toxic waste imported from Europe during wartime is very common.[15] In one study, Abu-Musa et al examined the effects of the Lebanese war on sperm parameters. In this study, semen samples obtained during the war were compared with post-war semen samples. The results indicated that the Lebanese civil war caused significant reduction of sperm concentration during wartimes. Besides, the percentage of normal morphology of sperm was reduced in the postwar period. Furthermore, volume and motility of sperm remained unchanged. The authors concluded that higher stress degree during the war played a pivotal role in these findings.

Concerning the Gulf War, three epidemiological studies have specifically examined infertility among veterans.[12-14] The UK male veterans of the first Gulf War showed high rates of infertility in comparison to non-deployed veterans. Moreover, trying to conception was also greater among UK male veterans of the first Gulf War. The same results were observed among Australian veterans of the first Gulf War. However, Ishoy et al did not find any significant change in reproductive hormones and fertility potential among Danish veterans of the Gulf War.[11] Only one epidemiological study especially evaluated infertility in relation to the Iran-Iraq war. However, Ladier-Fouladi did not find any effects for the Iran-Iraq war on Iranian fertility potential, and further studies are needed to better characterize the influence of psychological stress on semen quality parameters in the Iran-Iraq war.[44]

Effect of War on Environmental Degradation as a Factor Associated with Reproductive Health and Infertility

The prolonged war in Lebanon caused widespread environmental damage. Considerable toxic waste was illegally imported from abroad and dumped on Lebanon's soil. Heavy metals are known to be highly damaging agents to the reproductive system. Many Studies indicated that environmental contamination by heavy metals such as Cd, Zn, Pb, Mn, Se, and As could damage the production, maturation, motility, and fertilizing capacity of human spermatozoa.[45] Men living in urban areas have a greater reduction in ejaculation volume and sperm concentration in comparison to those living in rural districts. Thus, it can be suggested that chronic and low-level exposure to environmental contamination in war-torn countries can be associated with reproductive problems.[46]

Chemical Warfare Agents

Effect of Sulfur Mustard on Fertility

Sulfur mustard (SM or agent HD) is a lipophilic alkylating agent that has been widely used as a chemical warfare agent in several wars. Only few studies have so far examined the deleterious effects of SM on the fertility and reproductive system. These studies have shown that SM has negative effects on sperm quality and male fertility potential. Studies in animal models have shown that exposure to SM can damage the reproductive system in men and impair the production of sex hormones, eventually leading to sexual impotence. SM exposure can also affect sperm quality and quantity. Patients who have been exposed to SM have developed azoospermia and severe oligospermia.[23] Besides, abnormal morphology of sperm, reduction of sperm motility, reduced sperm count, abnormal viscosity of semen and reduction of semen volume have been reported in these patients.[19-21] In one study on patients who were exposed to SM during the Iran-Iraq war, semen analysis indicated that sperm abnormalities were observed in 38% of SM victims.[20] Studies on long-term SM exposure two decades after the exposure indicate that male infertility increased among exposed patients compared to non-exposed individuals.[23] Furthermore, severe adverse effects on the semen characteristics have been observed in the SM exposed men. Exposure to sulfur mustard analogues also causes changes in the levels of sex hormones such as gonadotropins and testosterone. Gonadotropins (FSH, LH) and testosterone are the major hormones in the spermatogenesis process.[19-23] Thus, changes in the levels of these hormones can eventually cause abnormal spermatogenesis. For example, the production of FSH in patients with a history of SM exposure was increased.[20] Besides, a long-term study by Azizi et al demonstrated deficiencies in androgen hormones and responsiveness to GnRH in these patients.[19,20] There was also a significant decrease in the levels of free testosterone[19] and dehydroepiandrosterone[20] in these patients. Testosterone plays a crucial role in spermatogenesis. The reduction in intra-testicular testosterone concentrations causes germ cell apoptosis in the seminiferous epithelium.[22] Due to the reduced testosterone levels caused by SM exposure, spermatogenesis is disrupted and apoptosis is induced in the germ cells, ultimately reducing sperm quality. Furthermore, low sperm counts and percentage of sperm abnormality are demonstrated to be significantly associated with a high FSH level. An elevated FSH level leads to abnormal spermatogenesis and may indicate primary testicular failure.[47] Several studies on testicular biopsies in SM-exposed patients revealed that spermatogenesis was arrested completely or relatively. Furthermore, atrophy of the germinal epithelium, intact Sertoli cells, and normal-appearing Leydig cells are increased.[47] Therefore, spermatogenesis seems to be the main target of the gonadal injury caused by SM. Sexual dysfunction is also very prevalent among SM victims, as in one study on Iranian men exposed to SM, 35% of them reported decreased libido.[27] Erectile dysfunction and premature ejaculation were also significantly increased among SM-exposed men.[25] Reduction of serum testosterone level can lead to these complications.[48]

Sulfur Mustard Induces Oxidative Stress

Reactive oxygen species (ROS) are naturally produced by aerobic cells. The cells have a defense line called antioxidants that can neutralize ROS. Oxidative stress occurs when ROS are produced excessively. Oxidative stress can damage cells.[49]

One of the important factors in poor sperm quality, sperm dysfunction, and male infertility is the increase in oxidative stress. A high percentage of infertile men show a high rate of seminal ROS which can damage the sperm DNA.[50-52] Spermatozoa are one of the most susceptible cell types to ROS.[50] Immature spermatozoa and leukocyte cells originating from the prostate and seminal vesicles can produce excessive ROS.[48] It has been clearly determined that by damaging the membrane lipids, DNA and proteins of sperm and altering the activity of enzymes and inducing cell death, ROS disrupt sperm quality, ultimately resulting in male infertility.[49]

SM exposure in the human body induces oxidative stress, which results in reduction in sperm quality and male infertility. It has been shown that SM can result in excessive production of ROS in the testicular tissue, adversely disturbing the structure and function of sperm.[53-55] It has been also reported that SM exposure can increase inflammatory reactions.[56,57]

Moreover, SM can increase the accumulation of inflammatory cells, including macrophages and neutrophils, thereby increasing the levels of inflammation chemical mediators such as interleukins and cytokines. The elevated levels of inflammation chemical mediators can increase the recruitment and activation of other leukocytes in the reproductive system. A high leukocyte number in the reproductive system can increase the level of ROS, which may exceed the potency of the antioxidant system and ultimately, result in oxidative stress in seminal plasma. ROS produced by SM-induced phagocyte cells cause induce inflammations, impaired spermatogenesis as well as apoptosis and low quality of sperm.[58] SM, in the reproductive tract, induces excessive production of ROS, disrupts the mitochondria function, increases the activity of enzymes producing ROS, and reduces seminal plasma antioxidants, including GSH and several antioxidant enzymes. Ultimately, SM causes an imbalance in stress oxidative level and antioxidant defense.[56]

Conclusion

In this study, we conclude that exposure to war can increase the risk of male infertility. In women, war leads to

menstrual dysfunction. It is not clear how war affects male and female infertility is not clear, but it seems that the increasing degree of stress during war can compromise the fertility potential. Physiological stress can affect fertility in direct and indirect ways.

Physiological stress can directly impair the function of the autonomic nervous, the neuroendocrine and the immune systems, whereas indirectly, it can cause change behaviors, for instance, smoking. Stress can also cause an abrupt change in the hormonal component of spermatogenesis. Physiological stress in women also disrupts menstrual cycles and ultimately disrupts women's fertility potential. So, psychological stress seems to induce female infertility during and/or after the war. The use of chemical agents during war also damages the male reproductive system. Recent studies show that SM can severely damage the reproductive function. SM has deleterious effects on sperm quality and male infertility. Oxidative stress-induced by SM exposure is one of the major mechanisms of impairment of reproduction potential in men. Oxidative stress can result in lower quality of sperm and ultimately, higher male infertility rates among SM-exposed patients.

Authors' Contribution

All authors contributed to the study conception and design. AB and FZ performed material preparation data collection. The first draft of the manuscript was written by AB and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflict of Interest Disclosures

None.

Ethical Statement

Not applicable.

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