Review

Effect of war on fertility: a review of the literature

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Abstract

The aim of this study was to review the existing literature on the effect of war on female and male fertility. A MEDLINE search for studies that included participants defined as infertile because they were unsuccessful in achieving a pregnancy after a year and studies that assessed the effect of war on semen parameters and menstrual dysfunction were performed. Twenty articles were included in this review. For female fertility, studies showed that women who were prisoners of war or who were living in areas exposed to bombardment had increased risk of menstrual abnormalities. For male fertility, the results were conflicting. The Vietnam War was not associated with difficulty in conception although one study revealed a decrease in sperm characteristics. Studies of male US and Danish 1990/91 Gulf war veterans showed no evidence of reduced fertility; however, studies of UK and Australian veterans reported increased risk of infertility. The Lebanese and Slovenian civil wars were associated with a decrease in sperm parameters. Exposure to mustard gas was also associated with abnormal semen parameters; however, exposure to depleted uranium had no effect on semen characteristics. Most of the studies examined had major limitations including recall bias and small number of cases included.

Keywords: *female infertility, male infertility, war*

Introduction

Compared with the many reports on adult health after service in the 1990/91 Gulf war, relatively few epidemiological studies have been conducted on reproductive outcomes. Even when reproductive outcomes were the focus of these few studies, their main outcomes revolved around spontaneous fetal death (Sato *et al.*, 1999; Kang *et al.*, 2001; Araneta *et al.*, 2003; Doyle *et al.*, 2004) and congenital malformations (Penman *et al.*, 1996; Cowan *et al.*, 1997; Kang *et al.*, 2001; Araneta *et al.*, 2003; Doyle *et al.*, 2004). In this context, very few studies have, specifically, examined the effect of war on infertility. Among these studies, the majority deal with male infertility in general and sperm parameters in particular, while very limited data on female infertility are available.

This scarcity of data pertaining to infertility can be primarily attributed to the fact that obtaining accurate epidemiological data on reproductive history is often methodologically challenging. There are few registers of infertility and most studies rely, by necessity, on self-reported information. Furthermore, a large sample size to enable meaningful interpretation of results is required.

The way in which war affects fertility is poorly understood. Many war-related exposures and traumas may put men/women at risk of infertility during or after a war period. In addition to multifarious reproductive toxins, other risk factors may include psychological stress and injury to the reproductive tract. This paper reviews the literature published to date about war and infertility.

Search procedures

MEDLINE was searched for studies published in English between January 1960 and December 2007 inclusive. The keyword used was 'war' and the search terms used were 'infertility', 'male infertility', 'female infertility', 'semen', 'sperm', 'menses,' 'menstrual cycle,' 'menstrual period,' 'menstrual irregularity,' ' menstrual aberration,' and 'amenorrhea'. The main outcome interest in the search was to review articles that assessed the effect of war on male and female fertility potentials. All studies that included participants defined as infertile if they had tried for a pregnancy unsuccessfully for more than a year were reviewed. Because the fertility potentials in males depend in part on sperm parameters and in females on menstrual regularity, studies that assessed the effect of war on semen parameters and menstrual dysfunction were also included in the review. In addition, studies that included either indigenous population exposed to war or military personnel deployed to war or combat zones were reviewed. Studies or data that evaluated other adverse reproductive outcomes, such as miscarriage, spontaneous abortion, ectopic pregnancies, fetal malformations, intrauterine growth retardation, and sex ratio modification were excluded from the review.

Based on the above criteria, 20 articles were included in this review; three were related to female fertility, and 17 were related to male fertility and are listed in **Table 1** and **Table 2** respectively.

War and female fertility

The literature about the effect of war on female fertility is scarce (**Table 1**). Most of the studies deal with menstrual cycle dysfunction. Very old reports showed the association between long periods of war and menstrual dysfunction. During World War II, many women who became prisoners had sudden onset of amenorrhoea that lasted for long periods of time (Whitacre and Barrera, 1944; Bass, 1947). A recent study evaluated the effect of internment in the German concentration camps during World War II on menstrual function and future fertility (Pasternak and Brooks, 2007). Five hundred and eighty Hungarian female survivors of concentration camps were included. Menstrual and reproductive histories of the women were obtained and analysed, comparing histories and events from pre-internment, internment, and post-internment periods of time. Amenorrhoea occurred in 94.8% of the women during encampment (95% CI 92.7–96.5%), with 82.4% experiencing cessation of menses immediately after internment (95% CI 76.9–85.6%). After liberation, all but 8.9% of the women resumed menstruation within the first year (95% CI 88.4–93.3%). Fecundity subsequent to liberation was not significantly affected by the imprisonment. The authors concluded that imprisonment in German concentration camps during the Holocaust resulted in abrupt changes in short-term menstrual function but little long-term physical damage to reproductive function.

Table 1. Summary of published papers on war and female infertility.

Reference	*Study setting and patients*	*Study design*	*Outcome*	*Results*	*Limitations*
Pasternak and Brooks (2007)	World War II: Hungarian female survivors of concentration camps	Interview survey	Menstrual and reproductive histories	Amenorrhoea occurred in 94.8% of the women during encampment. After liberation, 91% of the women resumed menstruation. Fecundity subsequent to liberation was not affected	Recall bias; no validation of reported menstrual difficulties
Blot and Sawada (1972)	Japan: Hiroshima and Nagasaki women exposed to radiation from the atomic bombs of 1945	Interview survey	Infertility	Exposure to high doses of atomic radiation did not impair subsequent fertility	Recall bias; no validation of reported fertility problems; accurate radiation dose not available
Hannoun *et al.*, (2007)	Lebanon: women whose villages were exposed to war in 1996. Divided into 3 groups based on staying or leaving war zone	Interview survey	Menstrual history at the beginning, 3 months after, and 6 months after war	Menstrual irregularities occurred in 35% of women staying in war zone and in 10% of women fleeing the area	Recall bias; no validation of reported menstrual irregularities

Table 2. Summary of published papers on war and male infertility.

Reference	*Study setting and patients*	*Study design*	*Outcome*	*Results*	*Limitations*
Stellman *et al.* (1988)	Vietnam: American Legionnaires who served during the Vietnam War in Southeast Asia and elsewhere	Self-administered questionnaire	Difficulties in having children	Neither combat nor Agent Orange exposure was associated with difficulty in conception	No clear definition of outcome; no validation of self-reported reproductive histories
DeStefano *et al.* (1989)	Vietnam: US deployed and non deployed veterans	Cohort population with computer-assisted semen analysis	Standard clinical semen analysis	Vietnam veterans had significantly lower mean sperm concentrations and normal morphology	Small study with low power; selection bias – both groups have normal semen analysis
Cowan *et al.* (1997)	US: male and female GWV compared with non-deployed veterans	Retrospective review of patient records	Rate of live births	Among men and women, the rates of live births for deployed and non-deployed veterans were similar	No direct assessment of infertility; no mention of possible treatment to achieve pregnancy
Ishoy *et al.* (2001)	Denmark: Danish male troops deployed to Gulf; reproductive health of GWV and NGWV	Interview survey with blood samples	Male reproductive health (reproductive hormones; self-reported infertility treatment due to childlessness)	No differences between groups in male reproductive hormones or reported fertility	Small study with low power; no validation of self-reported infertility treatment; hormone concentrations used to assess reproductive outcome
Sim *et al.* (2003)	Australia: male and female GWV and NGWV who had conceived a pregnancy or tried to conceive a child since 1991	Postal survey with clinic visit for a general health examination	Infertility	Male veterans increased risk of conception difficulties (RR = 1.4). Female veterans: no risk of conception difficulties	Small study – low power; no validation of reported conception difficulties – potential for reporting bias
Maconochie *et al.* (2004)	UK: male GWV and NGWV who had achieved a pregnancy, or had tried to conceive a child between January 1991 and August 1997	Postal survey with clinical validation of reported infertility problems	Infertility	Risk of reported infertility higher among GWV. Relative risks: infertility (no conceptions) 1.41; infertility (no live births) 1.50. Pregnancies fathered by GWV took longer to conceive (RR = 1.18)	Low response rate – possible selection bias; only 40% of cases of infertility clinically validated
Kelsall *et al.* (2007)	Australia: male GWV and NGWV	Self-administered postal questionnaire	Infertility	GWV reported slightly increased risk of fertility difficulties (OR 1.4; 95% CI 1.0–1.8)	Recall bias; no validation of data; sample size
Abu-Musa *et al.* (2007)	Lebanon: males providing semen samples at a university laboratory. Semen samples collected 1985–1989 (during war) were compared with those obtained 1991–1995 (post-war)	Retrospective review of patient records	Standard clinical semen analysis	Sperm concentration was significantly lower during war as compared with post-war period ($P < 0.001$)	Semen analyses were done in one laboratory – not representative of the general male population; inability to measure the level and type of stress during war time

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Kobeissi *et al.* (2007)	Lebanon: fertile and infertile males, distinguished by semen analysis and reproductive history	Clinic-based, case–control study, using reproductive history and risk factor interview data and laboratory-based semen analysis	Standard clinical semen analysis	Infertile male cases were more likely than fertile controls to have lived through the Lebanese civil war and to have experienced war-related trauma (OR 1.57)	Recall bias; clinic-based convenience sample was utilized instead of a population-based random sample; sample size
Zorn *et al.* (2002)	Slovenia: normozoospermic patients with semen analyses done before and after 1991 war	Clinic-based case control study using laboratory-based semen analysis	Standard clinical semen analysis	Significant fall in the total progressive motility ($P = 0.01$) and rapid progressive sperm motility ($P = 0.01$) after war	Clinic-based convenience sample was utilized instead of a population-based random sample; sample size; inability to measure the level and type of stress during war time
Azizi *et al.* (1995)	Iran: 16 men in the first three months and 42 men one to three years after injury with sulphur mustard	Cohort population with blood samples and standard clinical semen analysis	Male reproductive health (reproductive hormones and semen analysis)	Just after exposure testosterone and DS decreased while LH and FSH increased. Most patients followed for 1–3 years had sperm count below 30×10^6/ml, and increased FSH. Testicular biopsy showed complete or relative arrest of spermatogenesis	Sample size
Safarinejad (2001)	Iran: infertile patients exposed to sulphur mustard	Cohort population	Semen analyses, serum hormonal determinations, and genital examinations. Testicular biopsies done in 24 patients	Azoospermia and severe oligozoospermia were diagnosed in 42.5 and 57.5% of patients. Testicular biopsy showed selective atrophy of the germinal epithelium	Sample size
Ghanei *et al.* (2004)	Iran: couples exposed to sulphur mustard	Interviews, physical examination and reviews of medical records	Infertility	No increased risk of infertility	Selection bias; control group also exposed to sulphur mustard
McDiarmid *et al.* (2001, 2004, 2006, 2007)	USA: GWV exposed to DU	Medical examination, with blood, urine and semen samples	Standard clinical semen analysis	No significant change in semen characteristics	Extremely small study with very low power; identification of study subjects not random; no NGWV comparison group

Studies to determine both acute and latent effects of the atomic bombs of Hiroshima and Nagasaki upon pregnancy outcome and fertility have been conducted in Japan. In a fertility study spanning over a 16-year period (1945–1961), based on Japanese official family-registration records, Seigel (1966) found no significant differences in the ratios of numbers of live births to years of marriage among individuals residing in close proximity versus those residing further away from the hypocentres of the atomic explosions of 1945. A more detailed study that corroborated the results of previous studies examined fertility over a long period of time (18 years) and included calculation of radiation dose was published in 1972 (Blot and Sawada, 1972). Information collected on the reproductive histories of 2345 Hiroshima and Nagasaki women, subject to varying degrees of radiation exposure from the atomic bombs of 1945 by using personal interviews, showed that exposure to high doses (100+ rad) of atomic radiation did not impair subsequent fertility.

The data on fertility outcome and menstrual function of female veterans of the 1990/91 Gulf War is very limited. Women soldiers during Desert Storm, living the chronic stressful conditions of a prolonged war, suffered most from dysfunctional uterine bleeding (Petit, 1996), such as having heavier cycles or skipping their menses, especially during combat periods (Wardell and Czerwinski, 2001).

A recent study on the impacts of war on the menstrual cycle was conducted in Lebanon among civilian women living in small towns and villages in southern Lebanon, who were subjected to 16 days of shelling and bombardment in April 11–27, 1996 (Hannoun *et al.*, 2007). The women in this study completed a questionnaire related to their menstrual history at three different points: before the war, 3 months after, and 6 months after the war. The study divided the women into three main groups: group A included women who stayed in the war zone throughout the 16 days, group B included women who left the area within 1–2 days after the start of the war and group C included a group of women who were also living in south Lebanon but in an area not exposed to war (control group). At the time of war all women in the three groups had regular menstrual cycles, but 3 months later 35.3% of group A, 10.5% of group B, and 2.6% of group C had menstrual irregularities. These values were significantly different, indicating that exposure to war did lead to menstrual aberrations, especially in those exposed to prolonged periods of war. Six months later, although spontaneous resumption of regular cycles occurred in many women in the two groups exposed to war, significantly more women in group A continued to have menstrual irregularity compared with group B and C (18.6 versus 4.3 and 3.9% respectively). Women in groups A and B had a higher incidence of irregular cycles at 3 months compared with 6 months with $P < 0.031$ and $P < 0.006$ respectively. This did not hold true for women in group C.

War and male fertility

Vietnam War

Stellman *et al.* (1988) studied the relation between reproductive outcome and combat intensity and herbicide exposure among 6810 American Legionnaires who served during the Vietnam War (42% in Southeast Asia, 58% elsewhere). This study used a self-administered questionnaire to obtain details of reproductive history including difficulties in having children. Considering only ever-married men who said they tried to have children, 18.0% of those who served in Southeast Asia claimed to have had difficulty compared with 14.9% of controls (OR = 1.25, $P < 0.01$). However, this statistical significance was lost when the combat intensity and age were considered as confounding variables. The authors concluded that neither combat nor Agent Orange exposure was associated with difficulty in conception. The main limitation of this study was that the definition of difficulty in conception was not defined, and there is no validation of the self-reported reproductive histories.

DeStafano *et al.* (1989) measured the semen characteristics of 324 Vietnam veterans and compared them with a similar group of 247 veterans who did not serve in Vietnam. Measurements of sperm concentration, movement characteristics, and head dimensions were performed, using the Cellsoft computer-assisted semen analysis system. They found that Vietnam veterans had significantly lower mean sperm concentrations (64.8×10^6 sperm/ml for Vietnam veterans versus 79.8×10^6 sperm/ml for non-Vietnam veterans; $P < 0.05$), and Vietnam veterans were twice as likely to have sperm concentrations less than or equal to 20×10^6/ml (odds ratio = 2.7, 95% confidence interval = 1.3–5.7). Vietnam veterans also had a significantly lowered mean proportion of morphologically normal sperm heads (57.9 versus 60.8%). Despite differences in sperm characteristics, Vietnam and non-Vietnam veterans reported fathering similar numbers of children.

1990/91 Gulf War

The literature related to male fertility and war is summarized in **Table 2**. The first epidemiological study relating to fertility and the 1990/91 Gulf War was reported by Ishoy *et al.* (2001). The study was a cross-sectional study conducted during the period of January 1997 to January 1998 on 661 male Danish Gulf War Veterans (GWV) who had been deployed in the Persian Gulf, within the period of 2 August, 1990 until 31 December, 1997. A control group of 215 Danish military men, not deployed in the Gulf region, was selected with random matching by age and type of work. All participants underwent clinical and paraclinical examinations as well as were interviewed using a comprehensive questionnaire. Reproductive hormones were used as serum markers of male reproductive health status instead of semen parameters. Blood for FSH, LH, testosterone, serum hormone binding globulin (SHBG), and inhibin B measurements was taken. A serum inhibin B concentration of less than or equal to 80 pg/ml combined with a serum FSH of greater than or equal to 10 IU/l was used as a validated indicator of oligozoospermia (sperm count $<20 \times 10^6$ ml). No differences were found between GWV and controls with respect to any of the reproductive hormones measured, nor with respect to fertility. Based on these study results, the authors concluded that the biological reproductive health of male Danish GWV seemed to be unaffected by their engagement in the post war peace-keeping mission. No attempt was made to validate the self-reported reproductive histories, and the expected number of subjects included was very small and the power was consequently low.

The second study examined self-reported fertility status among Australian veterans, using a postal questionnaire (Sim *et al.*, 2003). Gulf War veterans were no more likely than the comparison group to have reported experiencing fertility difficulties prior to 1991, but more likely to have reported these occurring for the first time in the period 1991 or later. Of those subjects in both groups who reported fertility difficulties in the period 1991 or later, approximately half had sought infertility treatment and, of these, more than half had found causes for their fertility difficulties. Gulf War veterans who reported fertility problems post-1991 were more likely than the comparison group to report not having fathered a child since. The authors concluded that male Australian Gulf War veterans showed a 40% increased risk of having fertility problems. However, numbers for men in this study were small and the power consequently low.

The only study in the literature describing the effect of war on infertility among US veterans was by Cowan *et al.* (1997), who found no evidence of reduced fertility. Among men, the rate of live births (either in military or civilian hospitals) was 95.64 per 1000 for deployed veterans and 93.29 per 1000 for non-deployed veterans. Among the women the rate was 109.40 per 1000 for deployed veterans and 102.39 per 1000 for non-deployed veterans. Significantly more births were identified for the Gulf War veterans, both male and female, than for the non-deployed veterans.

The largest epidemiological study of infertility in GWV was the UK study (Maconochie *et al.*, 2004). This was a retrospective cohort study of the reproductive health of all UK armed forces personnel deployed to the Gulf region between August 1990 and June 1991 (51,581 men, 1230 women) and a comparison group who were in service at that time (January 1991) but were not deployed (51,688 men, 1236 women). Infertility was defined as having fertility problems and either never achieving a recognized pregnancy (type I infertility) or never achieving a pregnancy ending in a live birth (type II infertility). This study used a self-administered postal questionnaire to obtain details of reproductive history, but unlike the other studies, an attempt was made to verify and obtain further information on all reported fertility problems, including diagnostic details and a copy of the semen analysis results, if available, by contacting both male and female partners' General Practitioner or relevant clinician. Type I infertility was higher among Gulf veterans (odds ratio 1.41, 95% confidence interval 1.05–1.89); the effect was stronger for type II infertility (odds ratio 1.50, 1.18–1.89). Evidence was stronger for a more specific effect on risk of teratozoospermia (odds ratios 2.02, 0.79–5.14 for type I; 2.55, 1.03–6.30 for type II), and an association was also suggested between Gulf war service and risk of oligoasthenoteratozoospermia. Among planned pregnancies, those fathered by Gulf veterans took longer to conceive; 9.1% (845) took more than a year compared with 7.8% (528) of those fathered by non-Gulf veterans (adjusted odds ratio 1.18, 1.04–1.34). In conclusion, Maconochie *et al.* (2004) found a small increased risk of infertility among veterans of the Gulf war, strengthened by the finding that pregnancies fathered by Gulf veterans with no fertility problems reportedly took longer to conceive than did those fathered by non-Gulf veterans. Fertility problems among these veterans were mainly associated with teratozoospermia and oligozoospermia, suggesting apoptosis in the testicular germ cells, Sertoli cells, and/or Leydig cells following exposure to war-related chemicals. However, their analyses involved extremely small numbers (n = 132), so that no firm conclusions can be drawn. In addition, the study had a fairly low response rate (53% for GWV and 42% for non-GWV), but a study of non-responders provided no evidence of bias with respect to infertility, the prevalence of (self-reported) infertility among GWV and non-GWV being almost identical in responders and non-responders.

A recent study (Kelsall *et al.*, 2007) investigated whether male Australian GWV had increased adverse reproductive outcomes including fertility difficulties defined as difficulties for the participant and their partner getting pregnant despite trying for at least 12 months. The study groups for this analysis consisted of 1424 male veterans and 1548 male comparison group subjects. Participants completed a self-administered postal questionnaire. Male GWV reported slightly increased risk of fertility difficulties following the 1990/91 Gulf War (OR 1.4; 95% CI 1.0–1.8), but were more successful at subsequently fathering a child (OR 1.8; 95% CI 1.3–2.6). The study was limited by small numbers of adverse reproductive outcomes, the reliance on self-reported data, and the difficulties in attempting to validate the data with medical records.

War in Lebanon

The largest report that studied the effect of war on semen parameters was by Abu-Musa *et al.* (2007). Semen samples collected between 1985 and 1989 (during the Lebanese civil war) were compared with those obtained between 1991–1995 (post-war). A total of 4577 and 6205 specimen were collected in the war and post-war periods respectively. The sperm concentration was significantly lower during war as compared with the post-war period ($P < 0.001$). During war, more men had borderline oligozoospermia (count $11–20 \times 10^6$/ml) and fewer had a normal count ($>20 \times 10^6$/ml), which might imply that war affects individuals with borderline semen parameters rather than those with excellent semen parameters. However, the percentage of abnormal sperm morphology increased in the post-war period ($P < 0.001$). War had no significant effect on volume and motility.

The same group also assessed the effect of the Lebanese civil war on male infertility using a case-control study design (Kobeissi *et al.*, 2008). Two hundred and twenty men who were seeking IVF treatment were included in the study. The patients were divided into two groups according to their fertility status based on their semen analyses. The cases included 120 men who were considered infertile because of repeated abnormal semen analyses [World Health Organization (WHO), 1999]. The control group included 100 men with normal semen analyses, but who were seeking fertility treatment because of female factor infertility. Data were collected through a semi-structured interview schedule, which included baseline information on demographics and reproductive history. War exposures were assessed through men's self-report of participation in fighting, injury close residential proximity to bombing, and experiences of kidnapping, imprisonment, torture, and forced displacement. A war index was created to summarize men's often multiple war exposures, with higher scores reflecting higher numbers of exposures. Cases tended to report more exposures to war-related events than controls. Cases were more likely than controls to have participated in the war as fighters, resided in areas of heavy bombing during the war period, and were also kidnapped or were forced to flee from their homes. Sixty per cent of cases reported exposure to one or more war-related events, versus 49% of controls. In addition, 75% of cases who resided near areas of heavy bombing were oligospermic, as were 85% of the cases who were injured, 80% of cases who reported injuries to other family members, 92% of the cases who reported taking part in the war as combatants, 87% of the cases who reported being displaced from their homes, and 67% of the cases who reported being kidnapped or tortured. This case–control study demonstrated that exposure to war might be an independent risk factor for male infertility, when other potential confounders and covariates were controlled for. The odds of exposure to the Lebanese civil war were 1.57 times higher among cases than controls, a finding with borderline statistical significance. Cases were more likely than controls to report multiple exposures to war-related traumas, and the majority of these cases were found to be oligospermic. Furthermore, cases were significantly more likely than controls to have been exposed to the worst traumas of war, including participation in fighting, kidnapping and torture, and displacement from homes.

War in Slovenia

A short war took place in Slovenia between 26 June and 7 July, 1991. Zorn *et al.* investigated whether the psychological stress related to a short war in Slovenia induced changes in fertility, sex ratio at birth and semen quality characteristics (Zorn *et al.*, 2002). Semen analyses for 38 normozoospermic men attending an outpatient infertility clinic from May to September 1991 were also evaluated. A significant fall in the total progressive motility from 56% before the war to 52% after it ($P = 0.01$) and rapid progressive sperm motility from 39% before the war to 36% after it ($P = 0.01$) was noted, whereas sperm concentration and morphology did not change.

Toxins

Mustard gas

Azizi *et al.* (1995) investigated the acute and chronic effects of mustard gas in young men. Serum concentrations of total and free testosterone, dehydroepiandrosterone (DS), FSH, LH and prolactin were evaluated in 16 men in the first 3 months and testicular function in 42 men 1–3 years after injury. The serum total and free testosterone and DS concentrations were markedly decreased in the first 5 weeks after exposure. FSH, LH, prolactin, and 17 alpha-OH progesterone were normal in the first week, LH increased by the 3rd, and FSH and prolactin by the fifth week. All hormone concentrations had returned to normal by the 12th week after exposure. In 28 (66.7%) of 42 men examined 1–3 years after injury, the sperm count was less than 3×10^6 cells/ml and the FSH concentration was increased compared with normal men. This study demonstrates that the exposure to sulphur mustard results in very low androgen concentrations and hypo-responsiveness to gonadotrophin-releasing hormone (GnRH) in the first 5 weeks and normalization by the 12th week after injury. However, side effects of mustard on sperm cells persist and may cause defective spermatogenesis years after exposure.

In another study, Safarinejad (2001) evaluated 81 infertile patients who were injured with mustard gas during 1985–1988 in the Iran–Iraq War. Three semen analyses, serum hormone determinations (LH, FSH, and testosterone), and genital examinations were completed for all patients, as were testicular biopsies in 24 patients. Azoospermia and severe oligozoospermia were diagnosed in 42.5 and 57.5% of patients respectively. A significant decrease in sperm motility was noted in the infertile mustard gas-injured patients ($P < 0.02$). Hormone studies revealed an elevated plasma FSH concentration and normal plasma LH and testosterone concentrations. Testicular biopsy showed selective atrophy of the germinal epithelium, intact Sertoli cells, and normal-appearing Leydig cells. A dose-dependency was noted between severity of mustard gas exposure and adverse effects on fertility. Approximately 40% of those who were classed as 'severely injured' exhibited long-term fertility problems, whereas those with 'mild' gas-related injury, reported restored fertility within 3 months after referral. These data demonstrate the reversibility of testicular damage and a threshold limit of toxicity. The length of exposure time, proximity to the source, intensity of exposure, and wearing of protective clothing and a mask all had great implications in testicular damage.

The third study on mustard gas focused on fertility of Iranians exposed to an aerial bombardment with liquid mustard gas, of Sardasht, a Kurdish Iranian town, which took place on 27 July, 1987 (Ghanei *et al.*, 2004). In contrast to the two previously mentioned studies, results of this study failed to reveal an increased incidence of infertility among mustard-exposed couples compared with the worldwide average. The lack of significant differences in fertility rates between the two groups suggests that the dosage of mustard gas to which survivors were exposed were not gonadotoxic in humans. The authors concluded that in a population with similar exposure to mustard gas, fertility is not adversely affected by elevated concentrations of the agent during the timeframe in which conception is being actively attempted, suggesting that any mustard gas-associated impact on fertility may prove to be latent in nature

Depleted uranium (DU)

To date, six rounds of surveillance (1994, 1997, 1999, 2001, 2003, and 2005) have been conducted on a small number of US veterans exposed to DU during friendly fire incidents in the 1990/91 Gulf War (McDiarmid *et al.*, 2001, 2004, 2006, 2007). The numbers participating at each time point varied in size, but all are extremely small, between 29 and 50 GWV. The four overlapping studies involved GWV only, comparing either DU-exposed GWV having high (greater than or equal to 10 μg/g creatinine) urinary uranium concentrations with DU-exposed GWV having low (less than 10 μg/g creatinine) urinary uranium concentrations, or DU-exposed GWV with non-DU exposed GWV. Serum FSH, LH, prolactin, thyroid stimulating hormone (TSH), free thyroxine, and total testosterone were analysed. Evaluation of semen characteristics included: volume, sperm concentration, total sperm count, and functional parameters of sperm motility. Overall, despite persistent urine uranium elevations in these DU-exposed GWV for more than 15 years, no clinically significant difference in semen characteristics was found between groups at any of the time points. No statistically significant differences were observed in mean prolactin, FSH, LH, testosterone, free thyroxine or TSH values and all results were generally within the normal clinical range.

Discussion

The literature reviewed here demonstrates that exposure to war might be an independent risk factor for male infertility. For female infertility, there is insufficient information to make robust conclusions, although the weight of evidence to date does indicate that war might lead to menstrual dysfunction.

Proposed mechanisms of infertility

Male infertility

The way war affects male fertility is not clear, but it is believed that psychological stress plays an important role. War times are among the most stressful conditions that people face. The increased stress levels may be related to the direct impact of the war experience as well as to the deterioration in the physical infrastructure and socio-economic conditions. Most studies have indicated that stress has a negative impact on various parameters associated with semen quality, including sperm concentration, motility and morphology (Bents, 1985; Moghissi and Wallach, 1985; Giblin *et al.*, 1988). Stress associated with work place or family behaviour results in poorer sperm morphology and vitality (Gerhard *et al.*, 1992). However, motility seems to be one of the most sensitive characteristics. In men providing semen samples for an infertility work-up, an inverse relationship has been found between the level of perceived job stress and percentage of progressive spermatozoa (Bigelow *et al.*, 1998). The recent death of a close family member was associated with a reduction in straight-line velocity and percentage of progressively motile spermatozoa (Fenster *et al.*, 1997). Reduction of sperm motility was also related to the catastrophic Kobe earthquake (Fukuda *et al.*, 1998).

The mechanism by which psychological stress could affect semen quality is unclear. In general, a distinction is made between direct and indirect effects of stress. The direct effects refer to the effects mediated by the autonomic nervous system, the neuroendocrine system and the immune system, whereas the indirect effects imply those health changes resulting from changes in health behaviour, for instance smoking. The effects of stress may be via the hormonal component of spermatogenesis. There is evidence that such a phenomenon may be related to hormonal changes observed in the male during stressful events. Testicular biopsies obtained from prisoners awaiting sentencing, obviously under extreme stress, revealed complete spermatogenetic arrest in all cases (Steve, 1952). Milder forms of stress, such as that induced as a result of combat or surgery, have been shown to result in depressed testosterone concentrations in affected males (Kreuz *et al.*, 1972). This may be a result of activation of hormones from the hypothalamic–pituitary–adrenal axis, which are known to be elevated in response to stress (Guyton, 1989). McGrady (1984) noted that social stress in animals was related to diminishing testicular function via changes in LH and testosterone. Cui (1996) has attributed the lower semen volume and sperm concentration in a group of chronically stressed marmoset monkeys to lower concentrations of LH and testosterone. These changes appear to be mediated by endogenous opioids in the hypothalamic–pituitary–adrenal axis (Cui, 1996). There is evidence for the role of opioids in blocking the inhibitory effects of stress on LH and testosterone by the administration of naloxone, an opioid agonist (Norman and Smith, 1992). Changes in LH and testosterone may further affect the sympathetic and parasympathetic systems in acute stress situations, which directly affect testicular function and sperm quality.

Female infertility

The mechanism through which war affects menstrual cycles is not clear. Psychological stress is believed to play an important role. Most previous studies have indicated that different types of stress have a negative effect on the menstrual cycle. Changes in occupation were associated with changes in menstrual cycles (Jeyaseelan and Rao, 1995). Women in stressful jobs had more than double the risk for short cycle length compared with women not in stressful jobs (Fenster *et al.*, 1999). Among schoolgirls, 15.8% claimed that there was a correlation between school examinations and irregular menses (Demir *et al.*, 2000). This relationship between the psychosocial status of women and aberrations in menstrual cycles cannot be demonstrated in all cases exposed to stress (Hjollund *et al.*, 1999). This difference in response to stress may be explained by differences in population characteristics, study design, and differences in the assessment of psychosocial factors. The mechanism through which chronic stress can lead to menstrual irregularities is believed to be secondary to inhibition of the normal pulsatile GnRH secretion due to excessive hypothalamic activity of corticotrophin-releasing hormone in response to stress (Speroff and Fritz, 2005).

Another possible mechanism might be related to food deprivation that occurs during war time. It is well documented that female reproductive ability is profoundly hampered during undernutrition, which is manifested by menstrual irregularity or amenorrhoea and decreased fertility (Warren, 1983; Wynn and Wynn, 1993). A key factor in these responses may be the hypothalamopituitary–gonadal axis. During undernutrition at reproductive ages, the pattern of hypothalamic GnRH can return to a prepubertal state (Warren, 1983). As the adequate amplitude and pulsatility of GnRH is a prerequisite for normal menstruation (Filicori *et al.*, 1993), such a change may result in menstrual irregularity or amenorrhoea.

Toxins

Impaired male reproductive function may also be due to the use of reproductive toxicants during war. None of the studies discussed here has been able to examine risk according to particular exposures and so one cannot exclude the possibility of undetected adverse effects for small groups of veterans with high exposures to specific agents.

In the 1990/91 Gulf War, for example, some service members may have been exposed to vaccines, prophylactic medications, oil-well smoke, destruction of munitions and nerve agents, heat and other environmental stressors. They may also have been exposed to tobacco, alcohol, caffeine, medications and other factors not unique to deployment. Maconochie *et al.* reported fertility problems among UK veterans were mainly associated with teratozoospermia and oligozoospermia, suggesting apoptosis in the testicular germ cells, Sertoli cells, and/or Leydig cells following exposure to war-related chemicals mainly pyridostigmine bromide, the insect repellent *N,N*-diethyl-m-toluamide (DEET), and the insecticide permethrin (all of which are reported to have been present during the Gulf war) (Maconochie *et al.*, 2004). A report by the US General Accounting Office in 1994 had identified 21 potential reproductive toxicants and teratogens that were present during the 1990/91 Gulf War (GAO, 1988). The agents identified were present in smoke from oil fires, soil samples (arsenic, benzene, benzopyrene, cadmium, lead, mercury, nickel, toluene, xylene, di-n-butyl phthalate, hexachlorobenzene, hexachloroethane, pentachlorophenol, hexachlorocyclopentadiene), pesticides (carbaryl, diazinon, dichlorvos, ethanol, lindane, warfarin) and decontaminating agents (ethylene glycol monomethyl ether). Although most of these agents are potentially harmful with respect to female exposure, effects arising from paternal exposure to chemical and physical agents during the 1990/91 Gulf War were plausible. There was evidence from occupational epidemiology and animal studies that male exposure to heavy metals, solvents, paints and pesticides were associated with poor sperm quality, spontaneous abortion, birth defects and cancer in offspring (Welch *et al.*, 1988; Olshan *et al.*, 1991; Daniels *et al.*, 1997; Savitz *et al.*, 1997). Mustard gas and DU are the only toxins studied in relation to their effect on reproductive outcome in 1990/91 Gulf War veterans. Mustard gas is a lipophilic alkylating agent commonly referred to as the 'blister agent', due to its persistent and electrophilic properties. Its use has been documented in regional conflicts during the past 50 years, most recently in the Iran–Iraq War. It is characterized by its ability to cause changes in the structure of cell membranes, proteins as well as nucleic acids; it also interferes with cell division and DNA synthesis. Long-term exposure to mustard gas has been associated with increased rates of azoospermia and severe oligozoospermia, as a result of defective spermatogenesis. These increased rates are likely due to seminiferous epithelial atrophy in conjunction with chronic exposures. This testicular damage is reversible up to a certain threshold of toxicity. Mild mustard gas toxicity has been characterized by full recovery 3 months after exposure. However, upon the development of moderate oligozoospermia, chances of recovery are estimated to be only 20% (Safarinejad, 2001; Ghanei *et al.*, 2004).

Depleted uranium (DU) is a radioactive waste byproduct of the Uranium Isotope 235. DU is weakly radioactive with a radioactivity approximately 40% lower than that of natural uranium. The toxicity of DU is manifested both in terms of its chemical properties as well as its radioactive properties. It is characterized by the emission of alpha particles that have long penetrating abilities, specifically if ingested or inhaled. As such, its toxicity is directly proportional to route of exposure, particle solubility, contact time and route of elimination. The emergence of the awareness of the potential hazards of DU evolved following the first Gulf War, where it was used for the first time in 1991 (Domingo, 2001). Since then, medical surveillance follow-up programmes for veterans and active duty soldiers involved in military DU friendly-fire incidents have been conducted (McDiarmid *et al.*, 2001, 2004, 2006, 2007). In addition to short term inhalation and ingestion exposures to DU dust, some soldiers may receive shrapnel wounds in which fragments of DU metal become embedded in muscle tissue. This unique exposure pathway can give rise to chronic systemic exposure to DU as the DU metal fragments oxidize *in situ*, resulting in continued release of DU to the blood (Squibb and McDiarmid, 2006).

Literature on the reproductive health effects of DU is lacking. Most reproductive effects of uranium are based on its chemical nature and properties rather than on its radioactive action (Domingo, 2001). Chronic exposure to depleted uranium has been postulated to result in severe degeneration of the testis, depletion of germ cells, decreased testicular weight, increased testicular lesions, and necrosis of spermatocytes and spermatogonia. DU exposure may cause reproductive toxicity by (i) interacting with germ and other cells of the reproductive system, (ii) directly interacting with the central nervous system (CNS), resulting in abnormal reproductive behaviour or function, and (iii) modifying the CNS, leading to alterations in the secretion of hormones or gonadotrophins (Arfsten *et al.*, 2006). Another interesting discovery is that uranium, similar to other heavy metals, has oestrogenic activity (Raymond-Whish *et al.*, 2007). The authors suggested that uranium is an endocrine-disrupting chemical and populations exposed to environmental uranium should be followed for increased risk of fertility problems and reproductive cancers.

In Lebanon, heavy periods of bombing, importation of toxic waste from Europe, improper disposal of toxic waste in poorly designed landfills, open-air incineration of toxic waste, and haphazard dumping of solid waste in inadequate sanitary landfills were part and parcel of the civil war, contributed heavily to the environmental degradation of the country (Hamdan, 2002). These environmental challenges are of significant concern, given that they pose ongoing risks to air and water quality in the country (MOE-Lebanon, 2005). Heavy metals in particular, including lead, are well known reproductive toxicants. Whether heavy metals and other forms of long-term reproductive toxicity are impinging upon male fertility in Lebanon remains to be studied.

Limitations

The majority of the epidemiological studies described here are either cross-sectional surveys requesting information on events in the past or data linkage studies. The limitations of such studies mainly concern selection and information bias. Differential recall of infertility by the Gulf veterans or the comparison group is also a possibility. An information bias is inherent to observational studies measuring exposure that precede the study for 10 years, and therefore health events which occurred after exposures. In addition, studies done on GWV had a low response rate, raising the possibility of selective participation according to adverse reproductive outcome. Infertility is a condition that affects both partners and is a highly sensitive matter, particularly for men. It could be argued that Gulf veterans had more incentive to report infertility if they perceived that it might be related to their Gulf war service.

An additional problem in most of the studies is low statistical power due to the small number of cases included. In some studies, subjects were recruited exclusively from infertility clinics, where semen analyses were being done. Clinic-based study groups are rarely representative of the general male population, including those who were exposed to war-related trauma. It would have been interesting to follow the same cohort of individuals before and after the war to document a change in semen parameters.

Another major limitation of all of the studies relates to the inability to measure directly the level and type of stress involved during wartime. Relatively few of the studies provide detailed hormonal or clinical data on how degrees of stress may have affected semen parameters. In addition, confounding factors like male age, abstinence time, smoking, body mass index, urogenital diseases, and genital illnesses could not be assessed due to unavailability of this information. War itself might affect some of these factors indirectly through malnutrition or higher prevalence of infectious diseases.

The general inability accurately to measure specific environmental exposures in a combat environment that may adversely affect reproductive health is a further limitation of the study.

Conclusions and recommendations

Most of the studies reviewed here showed a possible association between war and infertility. In males war seems to affect sperm parameters and in females it might lead to menstrual dysfunction. Further detailed research to determine how the extent, intensity, and different types of warfare affect the reproductive health of both soldiers and civilians is clearly needed. Such types of war-related exposure cannot be taken lightly; various chemical toxicants with long half-lives may affect not only the fertility of current generations, but also of their offspring. Such findings must be further assessed through prospective cohort studies among men and women, both civilians and soldiers, who are facing war in different parts of the world. Specific and intensive focus on chemical measures is advisable, to determine possible causal mechanisms for male and female reproductive impairments.

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