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Papers

Infertility among male UK veterans of the 1990-1 Gulf war: reproductive cohort study

Noreen Maconochie, Pat Doyle, Claire Carson

Abstract

Objectives To examine the hypothesis that, theoretically at least, exposure to toxicants of the type present in the Gulf war could affect spermatogenesis, which might be observed as increased levels of infertility.

Design Retrospective reproductive cohort analysis.

Setting Male UK Gulf war veterans and matched comparison group of non-deployed servicemen, surveyed by postal questionnaire.

Participants 42 818 completed questionnaires were returned, representing response rates of 53% for Gulf veterans and 42% for non-Gulf veterans; 10 465 Gulf veterans and 7376 non-Gulf veterans reported fathering or trying to father pregnancies after the Gulf war.

Main outcome measures Failure to achieve conceptions (type I infertility) or live births (type II infertility) after the Gulf war, having tried for at least a year and consulted a doctor; time to conception among pregnancies fathered by men not reporting fertility problems.

Results Risk of reported infertility was higher among Gulf war veterans than among non-Gulf veterans (odds ratio for type I infertility 1.41, 95% confidence interval 1.05 to 1.89; type II 1.50, 1.18 to 1.89). This small effect was constant over time since the war and was observed whether or not the men had fathered pregnancies before the war. Results were similar when analyses were restricted to clinically confirmed diagnoses. Pregnancies fathered by Gulf veterans not reporting fertility problems also took longer to conceive (odds ratio for >1 year 1.18, 1.04 to 1.34).

Conclusions We found some evidence of an association between Gulf war service and reported infertility. Pregnancies fathered by Gulf veterans with no fertility problems also reportedly took longer to conceive.

Introduction

In late 1990 and early 1991 around 53 000 UK armed service personnel were deployed to the Gulf war. Compared with the many reports on adult health after service in the Gulf, relatively few epidemiological studies have been conducted on reproductive outcomes.[1–9] Only two of these studies specifically examined infertility.[5 8] The first study found no difference between Danish Gulf veterans and non-veterans in any of the reproductive hormones measured or with respect to fertility or adverse outcomes of pregnancy.[5] The second study found that Australian Gulf veterans were more likely than non-veterans to report difficulties with fertility but were subsequently more likely to father a pregnancy, perhaps because more sought treatment.[8] In both these studies, expected numbers were very small and power consequently low.

We now report findings relating to infertility from the only epidemiological survey of reproductive outcomes among UK Gulf veterans. Analyses of fetal death and congenital malformation have been reported elsewhere.[9]

Methods

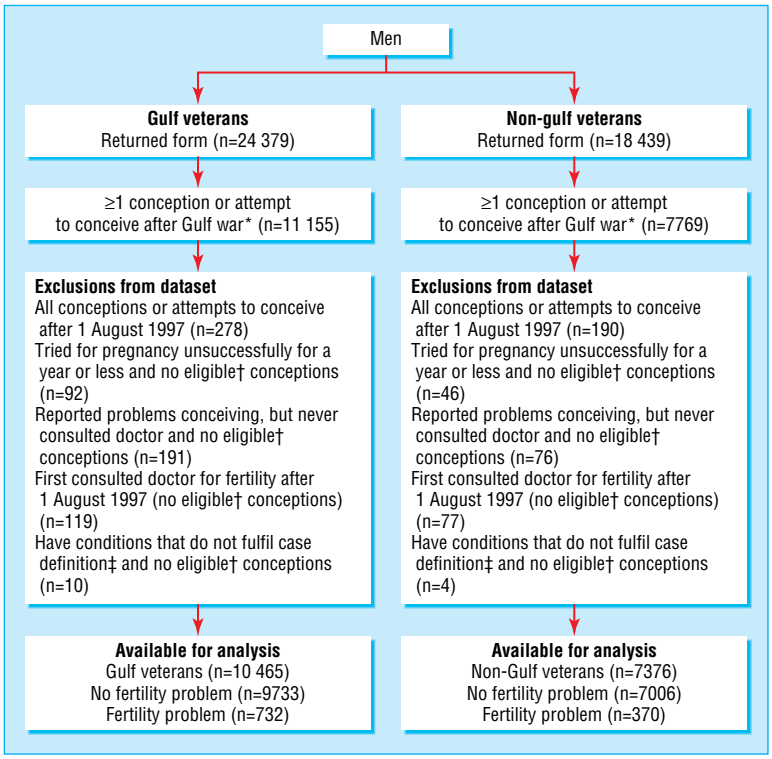
Main survey

Detailed information about the study is given elsewhere.[9 10] 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 (stratum matched on service, sex, age, fitness to be deployed, serving status, and rank) who were in service at that time (January 1991) but were not deployed (51 688 men, 1236 women). A postal questionnaire, sent from August 1998 (with reminders until early 2001), requested detailed information on reproductive history, including questions relating to infertility problems and their diagnosis and treatment. After adjustment for undelivered mail, response rates among men were 53% (24 379) for Gulf veterans and 42% (18 439) for non-Gulf veterans. Of theses men, 18 924 (44%) had fathered or tried unsuccessfully to father children since the Gulf war, 5711 (30%) of whom also reported pregnancies before the war.[10] Comparison of reproductive patterns among responders to the main study with those in a study of intensively traced non-responders provided no strong evidence of selection bias related to reproduction.[10] In particular, for both Gulf veterans and non-Gulf veterans the proportions consulting a doctor for infertility were almost identical to those among main study responders.

Investigation of infertility

The figure summarises the construction of the dataset. We restricted the analyses to men who had tried to have children since the Gulf war, regardless of whether they had conceived pregnancies before that. To minimise truncation effects, whereby participants whose first reproductive attempt was close to the start of the study had less time to conceive, we further restricted the analyses to men whose first post-Gulf conception or pregnancy attempt was before August 1997.

We defined participants as having fertility problems if they had tried for a pregnancy unsuccessfully for more than a year since the Gulf war and had consulted a doctor before 1 August 1997. We defined infertility as having fertility problems and either never achieving a recognised pregnancy (type I infertility) or never achieving a pregnancy ending in a live birth (type II infertility). We included participants as non-infertility cases if



Creation of dataset for analysis of infertility among male Gulf veterans and non-Gulf veterans. *After Gulf war deployment (Gulf veterans) or 1 January 1991 (non-Gulf veterans) and before start of main study (1 August 1998). †At least one pregnancy fathered after Gulf war and before 1 August 1997. ‡Congenital malformation of the urogenital system, sterilisation as a result of cancer treatment or injury, and unsuccessful reversal of (elective) sterilisation do not fulfil case definition for infertility

they had fathered at least one pregnancy after the Gulf war before the reported unsuccessful pregnancy attempt. If they had eligible conceptions we included (as non-infertility cases) participants who had tried for only a year or less or who had never consulted a doctor despite reporting problems, but otherwise we excluded them (fig).

Coding and clinical verification

Where relevant permission was available, we attempted to verify reported fertility problems by contacting both partners' general practitioner or relevant clinician. We requested diagnostic details, with a copy of semen analysis results if available. We received clinical information for similar proportions in the two groups (245/732 (33%) Gulf veterans, 117/370 (32%) non-Gulf veterans; P = 0.53 for difference). A copy of the actual semen analysis results (rather than the clinician's summary) was enclosed for similar proportions (90 (37%) Gulf veterans, 41 (35%) non-Gulf veterans; P = 0.56). These figures were higher for men with infertility. For the remainder we had no appropriate consent, no reply was obtained from the clinician, or relevant clinical notes could not be located. We based coding on information received from the clinician where available and otherwise on the participant's description only. We coded diagnoses in a standard way on the basis of World Health Organization definitions.[11] The three main indicators of semen quality were oligospermia (low sperm count) (at least one result of <20 million sperm/ml), asthenospermia (poor motility) (at least one result of $<50\%$ motility), and teratospermia (abnormal morphology) (at least one result of $>70\%$ abnormal forms).

Time to conception

We asked participants whether each pregnancy was planned and, if yes, how long it had taken to conceive, grouped as <3, 3-6, 7-12, and >12 months. We included in these analyses all pregnancies fathered after the Gulf war (and before 1 August 1997) by participants not reporting fertility problems.

Statistical methods

We used Stata statistical software for all analyses. All P values are two sided, and we took values less than 0.05 to indicate statistical significance.

We used logistic regression to estimate the effect of Gulf war service (or certain specific agents) on risk of infertility,[12] with non-Gulf veterans as baseline. Odds ratios relate to risk of the specified outcome with all eligible participants not having that outcome included in the denominator (whether or not they had other outcomes). We assessed statistical significance by using the likelihood ratio test.[12] We adjusted odds ratios for age of both participant and female partner at first consultation for infertility or post-Gulf conception, year of first consultation or post-Gulf conception, having fathered pregnancies before the war, and participant's service and rank at time of the Gulf war. We examined smoking at time of first consultation or conception and number of weekly units of alcohol consumed at survey (a proxy for alcohol consumption at first consultation or conception) in the modelling procedure, but neither acted as confounders, and we excluded them from the final models.

For time to conception the unit of analysis was a pregnancy; we estimated the effect of Gulf war service on risk of infertility by using logistic regression, with non-Gulf veterans as baseline. As more than one pregnancy reported by the same participant could be in the analysis, we used a robust method based on the "sandwich estimate" to calculate standard errors,[13] with Wald tests to test statistical significance of parameters.[14] We adjusted odds ratios in all analyses for pregnancy order, maternal age, year of conception, and service and rank at the time of the Gulf war. Smoking and alcohol again did not confound the effect of interest and were excluded from final models.

Table 1 Characteristics of men included in the analysis. Values are numbers (percentages) unless stated otherwise

	Gulf veterans (n=10 465)	Non-Gulf veterans (n=7376)
Age at survey (years)		
<30	2642 (25.3)	1491 (20.2)
30-34	4403 (42.1)	3134 (42.5)
35-39	2545 (24.3)	2046 (27.7)
≥40	875 (8.4)	705 (9.6)
Mean (SD)	33.4 (4.51)	33.9 (4.53)
Year of first attempt or conception after Gulf war*		
1991†	2296 (21.9)	1679 (22.8)
1992-3	3717 (35.5)	2691 (36.5)
1994-5	2726 (26.1)	1848 (25.1)
1996-7‡	1726 (16.5)	1158 (15.7)
Age at first attempt or conception after Gulf war* (years)		
<25	2807 (26.8)	1790 (24.3)
25-29	4535 (43.3)	3188 (43.2)
30-34	2363 (22.6)	1803 (24.4)
≥35	760 (7.3)	595 (8.1)
Mean (SD)	28.0 (4.50)	28.4 (4.55)
Age of wife or female partner§ at first attempt or conception after Gulf war (years)		
<25	3279 (31.8)	2116 (29.0)
25-29	4226 (41.0)	3026 (41.5)
30-34	2221 (21.6)	1708 (23.4)
≥35	581 (5.6)	449 (6.2)
Mean (SD)	27.0 (4.54)	27.2 (4.49)
Pregnancies before Gulf war		
All	2829 (27.0)	2492 (33.8)
Fertility problems after Gulf war¶		
All:	732 (7.0)	370 (5.0)
Reported pregnancies before Gulf war	117 (16.0)	72 (19.5)
Achieved recognised pregnancies	473 (64.6)	248 (67.0)
Achieved live births	376 (51.4)	204 (55.1)
No conceptions:	259 (2.5)	122 (1.7)
With pregnancies before Gulf war	45 (17.4)	27 (22.1)
No live births:	356 (3.4)	166 (2.3)
With pregnancies before Gulf war	61 (17.1)	35 (21.1)

*First unsuccessful attempt after Gulf war for those reporting fertility problems; first post-Gulf war conception for those reporting no fertility problems. Reproductive events assigned pre-Gulf or post-Gulf war status by date of first deployment (Gulf veterans) or 1 January 1991 (non-Gulf veterans and Gulf veterans where date of first deployment not known).
†135 Gulf veterans conceived pregnancies or first attempted unsuccessfully to have children in 1990, after deployment to the Gulf.
‡Attempts and conceptions included only up to 31 July 1997 (see methods).
§Excluding 158 Gulf veterans and 77 non-Gulf veterans with missing data.
¶Tried for a pregnancy after Gulf war without success for more than a year and consulted a doctor before 1 August 1997 about failure to conceive. With or without conceptions before Gulf war, but no conceptions after Gulf war before unsuccessful attempt. Excludes 14 men reporting fertility problems due to unsuccessful reversal of (elective) sterilisation, congenital urogenital anomaly, injuries (for example, paralysis), or cancer treatment.

Results

Study population

In total, 10 465 Gulf veterans and 7376 non-Gulf veterans who had conceived or attempted to conceive a child after the Gulf war satisfied the eligibility criteria. Year of first post-Gulf conception or attempted conception was similar in the two groups (table 1).

Infertility

Seven hundred and thirty two (7%) Gulf veterans and 370 (5%) non-Gulf veterans had consulted a doctor for fertility problems arising since the Gulf war (odds ratio 1.38, 95% confidence interval 1.20 to 1.60). More than 60% (n=721) of these men had succeeded in fathering one or more pregnancy, and more than 50% (n=580) had fathered one or more live birth by the time of survey (table 1). Prevalence of type I infertility was 2.5% (n=259) in Gulf veterans and 1.7% (n=122) in non-Gulf veterans; the equivalent figures for type II infertility were 3.4% (n=356) and 2.3% (n=166). For most men, this was primary infertility; only 45 (17%) Gulf veterans and 27 (22%) non-Gulf veterans with type I infertility had fathered one or more pregnancies before the war (table 1).

Among all participants reporting fertility problems we found no difference between Gulf veterans and non-Gulf veterans in total time trying unsuccessfully for a child—66% in each group (452/690 and 234/353) reported trying for more than two years (P=0.80) (not tabulated). Nor did we find a difference in length of time between first trying for a pregnancy and consulting a doctor (mean 14.0 (SD 0.41) months among Gulf veterans and 13.6 (0.57) months among non-Gulf veterans, P=0.53) (not tabulated). Slightly fewer Gulf veterans reported in vitro fertilisation or intracytoplasmic sperm injection treatment than non-Gulf veterans (107 (15%) *v* 60 (16%)), but this difference was not statistically significant (P=0.49) (not tabulated).

Table 2 describes the characteristics of men reporting type I infertility. Around 38% (n=144) were diagnosed as having one or more male infertility factor; 26% (n=67) of Gulf veterans and 25% (n=30) of non-Gulf veterans had a male factor alone. The proportions with a clear diagnosis of female infertility were similar in the two groups (44% (n=114) in Gulf veterans, 40% (n=49) in non-Gulf veterans; P=0.73 for difference).

Type I infertility was higher among Gulf veterans (odds ratio 1.41, 95% confidence interval 1.05 to 1.89); the effect was stronger for type II infertility (odds ratio 1.50, 1.18 to 1.89) (table 3). The effect did not vary with time since the war (P values for interaction 1.00 for type 1 infertility and 0.56 for type II infertility) or with whether the infertility was primary (no previous conceptions) or secondary (P values for interaction 0.83 for type I and 0.82 for type II).

We found only weak evidence of an association of Gulf war service with a general diagnosis of male factor infertility (odds ratio for type I infertility 1.18, 0.68 to 2.03), though the effect was slightly stronger for type II infertility (odds ratio 1.45, 0.98 to 2.14) (table 3). Evidence was stronger for a more specific effect on risk of teratospermia (odds ratios 2.02, 0.79 to 5.14 for type I; 2.55, 1.03 to 6.30 for type II), and an association was also suggested between Gulf war service and risk of oligoasthenoteratospermia. The numbers of cases were, however, extremely small. Analyses using only clinically verified cases produced very similar results (table 4).

We examined risk of infertility in relation to four self reported Gulf war exposures (vaccination against anthrax or plague, nerve agent pretreatment sets, depleted uranium, and pesticides) (table 5). A high proportion of men could not recall or did not know their exposure. Overall, the analyses revealed little or no evidence of an increased risk of infertility in relation to any specific exposure. We found some suggestion of an association between vaccination against anthrax or plague and infertility, particularly where a male factor was diagnosed, but numbers of unexposed cases for these analyses were extremely small, and all confidence intervals included 1.00.

Time to pregnancy

The 9733 Gulf veterans and 7006 non-Gulf veterans who did not have fertility problems had fathered 15 593 and 11 023 pregnancies respectively since the Gulf war (table 6). Pregnancies fathered by Gulf veterans were more often reported as unplanned (adjusted odds ratio 1.12, 1.05 to 1.19). Among planned pregnancies, those fathered by Gulf veterans took

Table 2 Characteristics of men classified as having type I infertility since Gulf war*. Values are numbers (percentages), percentages clinically confirmed

Characteristics	Gulf veterans (n=259)	Non-Gulf veterans (n=122)
Pregnancies before Gulf war	45 (17.4)	27 (22.1)
Clinical information† available		
Yes:	110 (42.5)	49 (40.2)
Actual semen analysis results provided with clinical information	41 (15.8)	21 (17.2)
Clinical summary of semen analysis only	69 (26.6)	28 (23.0)
No	149 (57.5)	73 (59.8)
Diagnosis‡		
Male factor diagnosed:	97 (37.5)	47 (38.5)
Male factor alone (no female factor found)	67 (25.9)	30 (24.6)
Male and female factors	30 (11.6)	17 (13.9)
No male factor:	80 (30.9)	35 (28.7)
Female factor diagnosed	44 (17.0)	19 (15.6)
No problem with either partner ("female factor unexplained")	36 (13.9)	16 (13.1)
Male factor not known:	82 (31.7)	40 (32.8)
Female factor diagnosed	40 (15.4)	13 (10.7)
No female factor found	6 (2.3)	3 (2.5)
Female factor not known	36 (13.9)	24 (19.7)
Male factor infertility§¶		
Azoospermia§	10 (3.9), 70.0	5 (4.1), 60.0
Oligospermia§	63 (24.3), 52.4	27 (22.1), 40.7
Asthenospermia§	39 (15.1), 71.8	19 (15.6), 89.5
Teratospermia§:	21 (8.1), 76.2	6 (4.9), 100
Oligoasthenospermia	13 (5.0), 69.2	4 (3.3), 100
Oligoteratospermia	6 (2.3), 50.0	0 (0), —
Asthenoteratospermia	3 (1.2), 100	3 (2.5), 100
Oligoasthenoteratospermia	8 (3.1), 87.5	2 (1.6), 100
Other male infertility factor§	2 (0.8), 100	1 (0.8), 0

*Tried for pregnancy after Gulf war without success for more than a year and consulted a doctor before 1 August 1997 about failure to conceive. With or without conceptions before Gulf war, but no conceptions after Gulf war previous to unsuccessful attempt. Excludes 14 men reporting fertility problems due to unsuccessful reversal of (elective) sterilisation, congenital urogenital anomaly, injuries (for example, paralysis), or cancer treatment.
†Clinical information relating to fertility problems requested from general practitioner or medical officer of both partners, including request for copy of semen analysis results, if available.
‡Where clinical evidence not available, diagnosis made from self report only.
§Participants may appear in more than one category if diagnosed as having more than one condition.
¶Clinically confirmed=summary from clinician with or without semen analysis results form, where patient had consented, details of general practitioner or medical officer were provided and current, and clinical notes were located.

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 to 1.34).

Discussion

Principal findings

We found a small increased risk of infertility associated with service in the 1900-1 Gulf war, which was strengthened when we extended the definition to include men reporting fertility problems who had fathered only pregnancies ending in fetal death. We found no strong evidence that the effect of Gulf war service was specific to men with a general diagnosis of male factor infertility, but we found some suggestion that both teratospermia and oligoasthenoteratospermia were increased. Further evidence consistent with a hypothesis of sperm damage was that for every male factor examined the relation with Gulf war service tended to strengthen when we included men who had fathered only

Table 3 Reported prevalence of infertility* after Gulf war. Values are numbers (percentages) unless stated otherwise

Outcome	Gulf veterans (n=10 465)	Non-Gulf veterans (n=7376)	Adjusted odds ratio† (95% CI)
Reported fertility problems after Gulf war‡:	732 (7.0)	370 (5.0)	1.38 (1.20 to 1.60)
No conceptions (type I)	259 (2.5)	122 (1.7)	1.41 (1.05 to 1.89)
No live births (type II)	356 (3.4)	166 (2.3)	1.50 (1.18 to 1.89)
Type I infertility after Gulf war—no conceptions			
Any male infertility factor§:	97 (0.9)	47 (0.6)	1.16 (0.74 to 1.82)
Azoospermia¶	10 (0.1)	5 (0.1)	0.95 (0.21 to 4.26)
Oligospermia¶	63 (0.6)	27 (0.4)	1.38 (0.75 to 2.53)
Asthenospermia¶	39 (0.4)	19 (0.3)	0.97 (0.51 to 1.85)
Teratospermia¶	21 (0.2)	6 (0.1)	2.02 (0.79 to 5.14)
Oligoasthenoteratospermia¶	*8 (0.1)*	*2 (0.03)*	*2.17 (0.43 to 10.89)*
Type II infertility after Gulf war—no live births			
Any male infertility factor§:	125 (1.2)	54 (0.7)	1.45 (0.98 to 2.14)
Azoospermia¶	10 (0.1)	5 (0.1)	0.95 (0.21 to 4.26)
Oligospermia¶	80 (0.8)	32 (0.4)	1.58 (0.94 to 2.65)
Asthenospermia¶	51 (0.5)	23 (0.3)	1.19 (0.68 to 2.08)
Teratospermia¶	26 (0.3)	6 (0.1)	2.55 (1.03 to 6.30)
Oligoasthenoteratospermia¶	*9 (0.1)*	*2 (0.03)*	*2.47 (0.51 to 12.00)*

*Infertility defined as trying for a pregnancy after Gulf war without success for more than a year and consulting a doctor before 1 August 1997 about failure to conceive (no conceptions after Gulf war before unsuccessful attempt); with no subsequent conceptions achieved (type I) or no live births achieved (type II). Excludes 14 men reporting fertility problems due to unsuccessful reversal of (elective) sterilisation, congenital urogenital anomaly, injuries (for example, paralysis), or cancer treatment.
†Adjusted for age of both participant and female partner at first consultation for infertility or first post-Gulf war conception (not infertile), year of first consultation or post-Gulf war conception, previous pregnancies (before Gulf war), and service and rank at time of Gulf war.
‡Whether or not conceptions subsequently achieved (that is, whether or not infertile, as defined in this paper).
§Excludes 136 Gulf veterans and 61 non-Gulf veterans for whom diagnosis not known.
¶Participants may appear in more than one category if diagnosed as having more than one infertility factor.

pregnancies ending in fetal death. These results should, however, be treated with extreme caution, given the small numbers and the fact that we were able to clinically validate only around 40% of cases of infertility. We also found that pregnancies fathered by Gulf veterans who did not report fertility problems took longer to conceive, although again the effect was not large

Consistency with other studies

Our results are consistent with the findings of a study of male Australian veterans, in which Gulf veterans had a 40% increased risk of having fertility problems.[8] However, the results conflict with a study of male Danish veterans, the only other study on this topic, which found no evidence of an effect of Gulf war service on markers of male fertility.[5]

Limitations

As discussed in previous reports,[9 10] our study does have a fairly low response rate, raising the possibility of selective participation according to adverse reproductive outcome. However, 90% of reasons given by both Gulf veterans and non-Gulf veterans in a study of non-responders were unrelated to adverse reproductive outcome, and the proportions of non-responding Gulf veterans and non-Gulf veterans who had consulted a doctor for infertility were almost identical to those among responders to the main study.[10]

Differential recall of infertility by the Gulf veterans or the comparison group is also a possibility, particularly as some evidence exists that miscarriage, particularly early miscarriage, is under-reported by male non-Gulf veterans in this dataset.[9] Infer-

Table 4 Prevalence of infertility* after Gulf war—clinically confirmed† cases only. Values are numbers (percentages) unless stated otherwise

Outcome	Gulf veterans (n=10 465)	Non-Gulf veterans (n=7376)	Adjusted odds ratio‡ (95% CI)
Type I infertility—no conceptions			
Any male infertility factor§:	58 (0.6)	26 (0.4)	1.18 (0.68 to 2.03)
Azoospermia¶	7 (0.1)	3 (0.04)	1.03 (0.17 to 6.17)
Oligospermia¶	33 (0.3)	11 (0.2)	1.76 (0.81 to 3.84)
Asthenospermia¶	28 (0.3)	17 (0.2)	0.86 (0.42 to 1.75)
Teratospermia¶	16 (0.2)	6 (0.1)	1.78 (0.69 to 4.60)
Oligoasthenoteratospermia¶	7 (0.1)	2 (0.03)	2.17 (0.43 to 10.89)
Type II infertility—no live births			
Any male infertility factor§:	74 (0.7)	32 (0.4)	1.33 (0.83 to 2.12)
Azoospermia¶	7 (0.1)	3 (0.04)	1.03 (0.17 to 6.17)
Oligospermia¶	41 (0.4)	15 (0.2)	1.68 (0.88 to 3.23)
Asthenospermia¶	37 (0.4)	21 (0.3)	1.02 (0.55 to 1.86)
Teratospermia¶	20 (0.2)	6 (0.1)	2.19 (0.87 to 5.51)
Oligoasthenoteratospermia¶	8 (0.1)	2 (0.03)	2.47 (0.51 to 12.00)

*Tried for a pregnancy after Gulf war without success for more than a year and consulted a doctor before 1 August 1997 about failure to conceive. No conceptions after Gulf war before unsuccessful attempt. Infertility defined as type I (no conceptions achieved) or type II (no live births achieved). Excludes 14 men reporting fertility problems due to unsuccessful reversal of (elective) sterilisation, congenital urogenital anomaly, injuries (for example, paralysis), or cancer treatment.
†Infertility cases with no clinical confirmation (clinician's summary or semen analysis results) excluded from these analyses. Unconfirmed diagnoses are not necessarily inaccurate but are merely cases where relevant permission was not given to consult clinical notes or clinical notes could not be located.
‡Adjusted for age at attempt, age of wife or partner at attempt (men), year of attempt, previous pregnancies (before Gulf war), and service and rank at time of Gulf war.
§Excludes 136 Gulf veterans and 61 non-Gulf veterans for whom diagnosis not known.
¶Participants may appear in more than one category if diagnosed as having more than one infertility factor.

Table 6 Pregnancies fathered by Gulf war veterans (n=9733) and non-Gulf war veterans (n=7006) not reporting fertility problems. Values are numbers (percentages) unless stated otherwise

	Pregnancies fathered		
	Gulf veterans (n=15 593)	Non-Gulf veterans (n=11 023)	Adjusted* odds ratio (95% CI)
Planned†:			
Yes	9968 (68.0)	7408 (71.5)	1.12‡ (1.05 to 1.19)
No	4700 (32.0)	2951 (28.5)	
Planned pregnancies only:			
Time to conception§:			
<3 months	5647 (61.0)	4410 (65.5)	1.18¶ (1.04 to 1.34)
3-6 months	1907 (20.6)	1224 (18.2)	
7-12 months	858 (9.3)	572 (8.5)	
>12 months	845 (9.1)	528 (7.8)	

*Adjusted for pregnancy order, maternal age, year of conception, and service and rank at time of Gulf war. Standard errors adjusted for repeated pregnancies fathered by same participant.
†Excluding 925 pregnancies reported by Gulf veterans and 664 by non-Gulf veterans with missing data.
‡Unplanned pregnancy as opposed to planned pregnancy in Gulf veterans relative to non-Gulf veterans.
§Excluding 711 planned pregnancies reported by Gulf veterans and 674 by non-Gulf veterans with missing data.
¶More than 12 months to conception as opposed to less than 12 months to conception in Gulf veterans relative to non-Gulf veterans.

tility 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. Unfortunately, few reliable estimates of infertility based on the UK population are available for comparison. Furthermore, predicting what the expected prevalence of infertility should be in comparison with other studies is difficult.

Interpretation

Notwithstanding possible limitations, the reported observations seem to be robust. The increases in risk did not decline with time since the Gulf war, nor were they different among men who had fathered children before the Gulf war. The constant effect over time argues in favour of either paternal germ cell mutation or other damage to spermatogenic stem cells or the testicular cells necessary for supporting spermatogenesis. In previous work we

Table 5 Exposures during the Gulf war—male Gulf veterans only

	Type I infertility after Gulf war		Type II infertility after Gulf war		Male factor infertility after Gulf war, type I		Male factor infertility after Gulf war, type II	
Exposure	Prevalence (No (%))	Adjusted* odds ratio (95% CI)	Prevalence (No (%))	Adjusted* odds ratio (95% CI)	Prevalence (No (%))	Adjusted* odds ratio (95% CI)	Prevalence (No (%))	Adjusted* odds ratio (95% CI)
Vaccination against anthrax, plague, or both†								
No	9/526 (1.7)	1.00	12/526 (2.3)	1.00	4/521 (0.8)	1.00	5/521 (1.0)	1.00
Yes	189/7801 (2.4)	1.16 (0.50 to 2.71)	269/7801 (3.5)	1.63 (0.78 to 3.37)	73/7705 (1.0)	2.95 (0.40 to 22.00)	95/7705 (1.2)	2.68 (0.64 to 11.21)
Pyridostygmine bromide tablets (NAPS)‡								
No	33/1514 (2.2)	1.00	47/1514 (3.1)	1.00	10/1496 (0.7)	1.00	15/1496 (1.0)	1.00
Yes	218/8689 (2.5)	1.06 (0.63 to 1.79)	299/8689 (3.4)	1.14 (0.75 to 1.71)	84/8580 (1.0)	1.57 (0.61 to 4.07)	106/8580 (1.2)	1.24 (0.62 to 2.48)
Depleted uranium§								
No	133/5624 (2.4)	1.00	176/5624 (3.1)	1.00	46/5561 (0.8)	1.00	60/5561 (1.1)	1.00
Yes	15/937 (1.6)	0.74 (0.37 to 1.51)	28/937 (3.0)	1.26 (0.78 to 2.03)	1/922 (0.1)	0.25 (0.03 to 1.84)	4/922 (0.4)	0.70 (0.25 to 2.02)
Pesticide¶								
No	56/2438 (2.3)	1.00	75/2438 (3.1)	1.00	16/2414 (0.7)	1.00	20/2414 (0.8)	1.00
Yes	143/6052 (2.4)	0.84 (0.53 to 1.34)	204/6052 (3.4)	1.03 (0.72 to 1.48)	58/5974 (1.0)	1.02 (0.46 to 2.25)	76/5974 (1.3)	1.36 (0.71 to 2.59)

NAPS=nerve agent pretreatment sets tablets (antichemical warfare nerve agent prophylaxis).
*Adjusted for age of both participant and female partner at first consultation for infertility or first post-Gulf conception (not infertile), year of first consultation or post-Gulf conception, previous pregnancies (before Gulf war), and service and rank at time of Gulf war.
†With or without pertussis adjuvant. Excludes 2138 (20.4%) Gulf veterans with no information on this exposure. Denominators for prevalence are all participants answering "no" or "yes" (as appropriate) to vaccination against anthrax, plague, or both; exposure not known excluded; diagnosis not known also excluded from denominators for analyses of male factor infertility.
‡Excluding 262 (2.5%) Gulf veterans with no information on this exposure. Denominators for prevalence are all participants answering "no" or "yes" (as appropriate) to having taken NAPS tablets; exposure not known excluded; diagnosis not known also excluded from denominators for analyses of male factor infertility.
§Excluding 3904 (37.3%) Gulf veterans with no information on this exposure. Denominators for prevalence are all those answering "no" or "yes" (as appropriate) to exposure to depleted uranium; exposure not known excluded; diagnosis not known also excluded from denominators for analyses of male factor infertility.
¶Excluding 1975 (18.9%) Gulf veterans with no information on this exposure. Denominators for prevalence are all participants answering "no" or "yes" (as appropriate) to exposure to pesticides; exposure not known excluded; diagnosis not known also excluded from denominators for analyses of male factor infertility.

What is already known on this topic

Relatively few epidemiological studies have examined reproductive outcomes in veterans of the 1990-1 Gulf war, and only two of these have specifically examined infertility

One study found no effect of Gulf war service on reproductive hormones or reported fertility; the second found that male Gulf veterans were more likely than the comparison group to report difficulties with fertility

In both of these studies expected numbers were small and power consequently low

What this study adds

Male UK veterans of the 1990-1 Gulf war had a small increased risk of reported infertility

Pregnancies fathered by veterans of the 1990-1 Gulf war who did not report fertility problems were reported to take longer to conceive

These results should be interpreted with caution, and we cannot at this stage conclude that the associations are causal

found no increase in genetic syndromes and chromosomal anomalies in the offspring of Gulf veterans, but we did observe an increase in reported miscarriage.[9] Furthermore, the suggestion in our data that the effect of Gulf war service might be strongest for teratospermia, and perhaps oligoasthenoteratospermia, is consistent with findings of apoptosis in testicular germ cells, Sertoli cells, and Leydig cells in rats subjected to combined exposure to pyridostigmine bromide, the insect repellent DEET, and the insecticide permethrin (all of which are reported to have been present during the Gulf war).[15] Having said that, we must be aware that some of our analyses involved extremely small numbers, so that no firm conclusions can be drawn.

Gulf war veterans are known to report more illnesses than non-veterans.[16] To what extent these illnesses have a direct effect on infertility and time to conception is not known, but Gulf related illness may have played a part in our findings. The role of stress related conditions may be particularly important, although we could not investigate this further with the data available.

Conclusion and recommendations

This study found evidence of a small increased risk of infertility among veterans of the 1990-1 Gulf war, strengthened by the finding that pregnancies fathered by men with no fertility problems reportedly took longer to conceive than did those fathered by non-Gulf veterans. Put together with the previous finding of increased risk of miscarriage among pregnancies fathered by male UK Gulf veterans,[9] we feel that the results of this study justify further research into the reproductive health of men deployed to the Gulf region, including a prospective investigation of semen quality and fecundability among veterans of the recent conflict in Iraq.

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Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, University of London, London WC1E 7HT
Noreen Maconochie *senior lecturer in epidemiology and medical statistics*
Pat Doyle *reader in epidemiology*
Claire Carson *research assistant*
Correspondence to: N Maconochie noreen.maconochie@lshtm.ac.uk