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The study of reproductive outcome and the health of offspring of UK veterans of the Gulf war: methods and description of the study population

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Abstract

Background: The aim of this study is to determine whether Gulf war veterans and their partners are at increased risk of adverse reproductive events and whether their children have increased risk of serious health problems. Methods and response to the study are reported here.

Methods: This was a retrospective cohort study of reproduction among UK Gulf war veterans, with a comparison cohort of Armed Service personnel who were not deployed to the Gulf. Reproductive history and details of children's health was collected by means of a validated postal questionnaire. A separate study of non-responders was conducted.

Results: Questionnaires were returned by a total of 25,084 Gulf war veterans (24,379 men) and 19,003 (18,439 men) subjects in the comparison group. After adjusting for undelivered mail the response rate was 53% for Gulf war veterans and 42% for non-Gulf veterans among men, 72% and 60% among women. Data from the non-responder study suggests that failure to respond to the main survey was largely unrelated to reproduction. 11,155 (46%) male Gulf war veterans and 7,769 (42%) male non-Gulf war veterans had conceived, or attempted to conceive, since the Gulf war. They reported 16442 and 11517 pregnancies respectively in that period. For women, 313 (44%) Gulf veterans and 235 (42%) non-Gulf veterans reported 484 and 377 pregnancies respectively conceived since the Gulf war.

Conclusions: This survey enabled collection of information on a range of reproductive outcomes from veterans of the Gulf war and a suitably matched comparison cohort. Although the response rate for men was disappointing, selection bias related to reproduction does not appear to be strong in these data.

Background

The United Kingdom deployed over 53,000 Armed Serv-

ice personnel to the Gulf war in 1990 and 1991. Anecdotal reports of morbidity appeared soon after the end of the

conflict, including US media articles highlighting problems with reproduction and pregnancy outcome [1–4]. A report by the U.S. General Accounting Office in 1994 identified 21 potential reproductive toxicants and teratogens present during the Gulf war and listed agents that were present in smoke from oil fires, soil samples, pesticides, and decontaminating agents [5]. In addition, a high proportion of deployed personnel were exposed to multiple vaccinations, including those for plague and anthrax, and some also took pyridostigmine bromide (anti-chemical warfare nerve agent prophylaxis, or NAPS) tablets.

Obtaining accurate epidemiological data on reproductive history is methodologically challenging. There are few registers of early fetal death or infertility and most studies rely, by necessity, on self-reported information. Validation of self-reported adverse outcomes of pregnancy, although ideal in principle, can be complex and time-consuming in practice. Furthermore, the rarity of certain outcomes of interest, such as specific congenital malformations, requires large sample sizes to enable meaningful interpretation of results. It is thus not surprising that, compared to the many reports on adult health following service in the Gulf, relatively few epidemiological studies have been conducted on reproductive outcome [6–12].

The two main outcomes of interest have been spontaneous fetal death (miscarriage, stillbirth) [10–12] and congenital malformations [6–12]. With one exception [12], published reports to date do not support a hypothesis of major damage to reproduction or of deleterious effects on the health of their offspring. However certain studies were limited by the lack of a suitable control group [6] or by exclusion of deployed personnel who had left the Armed Services [7,8]. Others investigated congenital malformations in livebirths only and thus excluded cases which ended as fetal deaths or medical terminations of pregnancy [7–9]. The most recent report on US veterans [12] found higher reported rates of fetal loss and congenital malformations in offspring reported by both male and female Gulf veterans compared to a group of Armed Service personnel who were not deployed to the Gulf. This study included abnormalities diagnosed in stillbirths and medical terminations of pregnancy, but did not attempt to validate self-reported conditions using medical notes.

We now report on an epidemiological survey of reproductive outcome and the health of offspring of UK veterans of the Gulf war. This is the only study of reproductive outcome among UK Gulf war veterans and the first to approach all veterans (and a matched comparison group). The study design was developed from several other large epidemiological surveys of reproductive outcome which showed that a postal method could be used to obtain full reproductive histories from large study populations [13–

16]. The design of the study, together with response rates and description of the study population is presented in this report. Further reports on fetal death, congenital malformations, illness and mortality in offspring, and infertility in veterans, will follow.

Methods

This was a retrospective cohort study of reproduction and pregnancy outcome.

Gulf War Veterans cohort (GWV)

The study cohort consisted of all UK armed forces personnel deployed to the Gulf area at any time between August 1990 and June 1991. 520 subjects were excluded for security reasons (such as membership of the special forces), and 228 subjects had their status changed to non-Gulf deployed after more information was received from their questionnaires. 96 subjects were excluded because they did not serve in the Gulf with the UK armed forces. A total of 51,581 men and 1,230 women formed the GWV cohort for this study (Table 1).

Comparison cohort (NGWV)

The comparison cohort comprised demographically similar Armed Service personnel, who were in service on 1st January 1991 and were appropriately fit, but were not deployed to the Gulf. This group was stratum-matched to the GWV on Service (Royal Navy (RN), Army and Royal Air Force (RAF)), sex, age (in 5-year groups), serving status at the time of the Gulf war (regular, reservist), and rank (officer, other ranks). 204 subjects had their status changed to GWV after receiving more information from them. A total of 51,688 men and 1,236 women made up this comparison group (Table 1). Major deployments within this cohort between August 1990 and June 1991 included Northern Ireland, Germany, Falklands, Belize, Northern Iraq/Turkey, Cyprus, Gibraltar and Hong Kong.

Survey method

Address information

The Ministry of Defence (MoD) supplied name, date of birth, sex, Service, date of joining and leaving (for discharged personnel) the armed forces, and last known address for all surviving cohort members. Pilot studies showed that address information held by the MoD for discharged personnel was inaccurate (21% pilot mail was returned undelivered). To reduce postal costs we therefore sent a brief introductory letter prior to the main mailing in which we asked recipients to inform us (by Freephone or reply-paid mail) if the addressee was no longer at that address (with new details if known). The MoD regularly provided current known address and serving status from discharge, military pensions and British Forces Post Office databases, and we also piloted and developed a method of obtaining address information directly from Health Au-

Table 1: Composition of armed forces cohort deployed to the Gulf (GWV) and matched comparison group (NGWV) ¹

| | MEN | | | | WOMEN | | | |
|---|--------------|--------------|-------------------|------------|-------------|--------------|-------------------|--------------|
| | GWV | | NGWV ¹ | | GWV | | NGWV ¹ | |
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Total | 51581 | (100) | 51688 | 100 | 1230 | (100) | 1236 | (100) |
| CHARACTERISTICS AT TIME OF GULF WAR²: | | | | | | | | |
| Age | | | | | | | | |
| <20 | 6376 | (12) | 6201 | (12) | 99 | (8) | 98 | (8) |
| 20–24 | 18318 | (36) | 18269 | (35) | 422 | (34) | 419 | (34) |
| 25–29 | 12322 | (24) | 12367 | (24) | 373 | (30) | 376 | (30) |
| 30–39 | 11756 | (23) | 11962 | (23) | 239 | (19) | 243 | (20) |
| > = 40 | 2809 | (5) | 2889 | (6) | 97 | (8) | 100 | (8) |
| Mean (SD) | 27.0 (6.84) | | 27.1 (7.22) | | 27.6 (6.86) | | 27.7 (7.29) | |
| Service | | | | | | | | |
| RN | 5747 | (11) | 5987 | (12) | 70 | (6) | 69 | (6) |
| Army | 35979 | (70) | 35877 | (69) | 955 | (78) | 964 | (78) |
| RAF | 9855 | (19) | 9824 | (19) | 205 | (17) | 203 | (16) |
| Serving status | | | | | | | | |
| Regular | 50780 | (98) | 50966 | (99) | 919 | (75) | 977 | (79) |
| Regular or Volunteer (TA / RNR / RRAF) reservist | 801 | (2) | 722 | (1) | 311 | (25) | 259 | (21) |
| Rank | | | | | | | | |
| Officer | 5396 | (10) | 5707 | (11) | 443 | (36) | 451 | (36) |
| Other ranks | 46185 | (90) | 45981 | (89) | 787 | (64) | 785 | (64) |
| CHARACTERISTICS AT START OF MAIN STUDY (1ST AUGUST 1998): | | | | | | | | |
| Age | | | | | | | | |
| <30 | 15676 | (30) | 15642 | (30) | 284 | (23) | 317 | (26) |
| 30–39 | 25552 | (50) | 25314 | (49) | 704 | (57) | 669 | (54) |
| > = 40 | 10353 | (20) | 10732 | (21) | 242 | (20) | 250 | (20) |
| Mean (SD) | 34.6 (6.85) | | 34.7 (7.22) | | 35.2 (6.85) | | 35.3 (7.29) | |
| Serving status | | | | | | | | |
| Regular (service address) | 24675 | (48) | 23585 | (54) | 293 | (24) | 313 | (25) |
| Discharged / reservist ³ (home address) | 26906 | (52) | 28103 | (46) | 937 | (76) | 923 | (75) |
| CHARACTERISTICS AT END OF STUDY (31ST MARCH 2001): | | | | | | | | |
| Serving status | | | | | | | | |
| Regular (service address) | 20733 | (40) | 19584 | (38) | 225 | (18) | 253 | (20) |
| Discharged / reservist ³ (home address) | 30848 | (60) | 32104 | (62) | 1005 | (82) | 983 | (80) |

¹In active service, or on the regular or volunteer reserve list at 1st January 1991; fit to go into combat, but not deployed to the Gulf. Stratum-matched on sex, age, service and rank to the GWV. ²At 1st January 1991, or at time of first deployment if known (GWV responders). ³Personnel discharged from regular service and regular or volunteer reservists.

thority databases. By the end of the study in March 2001 60% of the GWV and 63% of the NGWV had left the armed forces (or were on the reserve lists), and hence could not be reached via a Service address (Table 1). Discharged personnel were found to be extremely mobile, and by the end of the study we had collected up to 10 different addresses per subject (median 2).

Conduct of the survey

The authors developed the survey methods in previous large-scale cohort studies of reproductive outcome [13–16]. Having ascertained their vital status, packages containing a questionnaire and accompanying information

leaflet were sent to all cohort members using the most up-to-date address held within the database. Up to two reminders were sent to each new address after 6 weeks had elapsed. For in-service personnel, the second reminders were collated by unit and sent via commanding officers. In order to promote the study, posters were placed within all armed forces units and British Legion establishments, and numerous radio and television programmes advertised the launch of the study. Throughout the study we maintained close liaison with Gulf war veteran groups, armed forces welfare groups, and resettlement programmes. A freephone helpline was maintained by a nurse throughout the study, and a total of 5,487 calls were

logged (4,045 GWV 1,442 NGWV). The majority of calls and letters to the study team related to queries about the study and/or questionnaire prior to returning it completed, and/or requests for counselling. Many were from GWV for whom we did not have a valid address, who were identifying themselves for the study following publicity campaigns

The questionnaire

Our postal questionnaire requested details of all liveborn children, including name, sex, date and place of birth, birthweight, any congenital defects or serious medical conditions ever experienced, and date of death if appropriate. Also requested were details about infertility and any adverse pregnancy outcomes (miscarriage, stillbirth, ectopic pregnancy, hydatidiform mole, missed abortion) or terminations of pregnancy, including date of pregnancy end, gestation, whether any abnormalities were detected in the fetus and sex of fetus if known. Questions on service history, smoking history, current alcohol consumption, and details of vaccinations and exposure to specific chemicals and environmental factors during the Gulf war (1990–91 for NGWV) were included. We also collected information on the study participant's current health, and that of their partner and on changes in health status since 1991. Further, we asked for details (including Gulf war service) of any partner with whom the subject had conceived pregnancies who had ever served in the Armed Forces. Missing information was checked by letter and/or telephone.

Intensive Tracing Study (ITS)

Despite considerable effort spent on attempts to trace and contact all members of the two cohorts, a sizeable proportion of the subjects did not respond after two reminders to the same address, or their mail was returned undelivered. Further tracing and advertising work would have had considerable time and cost implications and the funders suggested that further large-scale mailing would not be cost-effective. Thus it was decided to stop the study and conduct an in-depth survey to explore response bias. A stratified (by Gulf deployment, rank and age) random sample was selected of 2931 men who had not responded after two reminders to the same address (ITS-NR), and 925 men whose questionnaire had been returned to us undelivered (ITS-UN). Several methods were then employed to attempt to trace and contact these individuals. For those still in service (1,203 subjects) a covering letter from a high-ranking officer encouraging response was enclosed with the questionnaire, having double-checked addresses with relevant commanding officers. For discharged personnel and reservists we used telephone databases to trace home telephone numbers then phone the participants (578 subjects); computerised electoral registers to trace and/or verify addresses prior to mailing (771 subjects);

and registered mail for delivery (304 subjects). We also requested the Driver and Vehicle Licensing Agency (DVLA) to address packages to 1000 discharged personnel and post them on our behalf. All except the DVLA sample were sent a shortened version of the questionnaire, requesting reproductive history only, with additional questions about reasons for previous non-participation or current refusal. Some of the responders subsequently agreed additionally to fill in the full questionnaire.

Study pregnancies

Subjects were asked for gestation at pregnancy end and whether the pregnancy was confirmed by a clinician. All pregnancies under 16 weeks were treated as singleton, regardless of number of fetuses/sacs reported because antenatal scanning (hence confirmation of multiple pregnancy) is not universal before that gestation. Dates of conception for each pregnancy were estimated as the date of pregnancy end minus gestation plus fourteen days. Where gestational age was not given (2% livebirths, 3% fetal deaths and 10% other outcomes among post-Gulf/1991 conceptions) it was estimated by the median for all other pregnancies of that type, for example 40 weeks (livebirth), 10 weeks (miscarriage) and 32 weeks (stillbirth). Pre- or post-Gulf deployment status was assigned to conceptions using reported dates of deployment (GWV) or 1st January 1991 (NGWV, and where exact dates of deployment for GWV were not known (3% of all pregnancies reported by GWV)). Pregnancies conceived after 8th November 1997 (less than 38 weeks before the first mailing) were excluded to avoid truncation effects resulting from pregnancies of short duration being more likely to be included than longer (primarily liveborn) ones.

Coding and classification of congenital malformations

All reported adverse health outcomes in the offspring of GWV and NGWV were coded to the 10th Revision of the International Classification of Diseases (ICD10) [17], the coder being blind to the deployment status of the parent. For analyses of congenital malformation, the condition could have been diagnosed in-utero, at birth, or at any time after birth. Fetal deaths below 16 weeks gestation were excluded because they are not systematically examined for abnormalities. All coding was checked by one of the authors (PD) without knowledge of the exposure status of the parent. Where there was limited information on a condition, coding was verified by an independent paediatrician. If more than one malformation per offspring was reported each case was scrutinised to ensure that specific syndromes were not missed. Individual codes were grouped for analysis based on the classification system used by the European Registry of Congenital Anomalies (EUROCAT) [18], with an additional grouping consisting of malformations in tissues originating from the embryonic cranial-neural crest. An extra grouping of metabolic

Table 2: Congenital Malformation groupings with ICD 10 codes

| | |
|---|--|
| Central nervous system | Q00.0–Q07.9 |
| Neural tube | Q00.0–Q01.9, Q05.0–Q05.9 |
| Hydrocephalus ¹ | Q03.0–Q03.9 |
| Remainder of CNS ¹ | Q02.0–Q02.9, Q04.0–Q04.9, Q06.0–Q07.9 |
| Eye, ear, face and neck ¹ | Q10.1–Q10.4, Q10.7–Q16.9, Q17.1, Q17.2, Q17.8, Q18.0 – Q18.9 |
| Eye | Q10.1–Q10.4, Q10.7–Q15.9, |
| Ear | Q16.0–Q16.9, Q17.1, Q17.2, Q17.8 |
| Remainder of Eye, Ear, Face, Nose | Q18.0–Q18.9 |
| Circulatory system | Q20.0–Q26.9, Q27.1–Q28.9 |
| Congenital malformations of heart | Q20.0–Q24.9 |
| Other malformations of circulatory system | Q25.0–Q26.9, Q27.1–Q28.9 |
| Respiratory system | Q30.0 – Q34.9 |
| Cleft lip/palate ¹ | Q35.0 – Q37.9 |
| Digestive system | Q38.0, Q38.2–Q45.9 |
| TOF & other malfs of large intest., rectum, anal canal ² | Q39.0 – Q39.9, Q42.0 – Q42.9 |
| Other malformations of digestive system | Q38.0, Q38.2–Q38.9, Q40.0–Q41.9, Q43.0–Q45.9 |
| Genital system | Q50.0–Q52.9, Q54.0–Q56.4 |
| Urinary system | Q60.0 – Q64.9 |
| Renal anomalies | Q60.0–Q61.9, Q63.0–Q63.9 |
| Urinary tract anomalies | Q62.0–Q62.9, Q64.0–Q64.9 |
| Musculo-skeletal system | Q65.0–Q65.8, Q66.0–Q66.4, Q66.6–Q66.7, Q67.0–Q70.0, Q70.2, Q70.4–Q75.9, Q76.1 – Q79.9 |
| Limb reduction | Q71.0–Q73.9 |
| Polydactyly and Syndactyly | Q69.0–Q70.0, Q70.2, Q70.4–Q70.9 |
| Other limb malformations | Q65.0–Q65.8, Q66.0–Q66.4, Q66.6–Q66.7, Q68.1–Q68.5, Q74.0–Q74.9 |
| Anomalies of diaphragm, exomphalos, gastrochisis | Q79.0–Q79.5 |
| Other musculo-skeletal anomalies | Q67.0–Q67.8, Q68.0, Q68.8, Q75.0–Q75.9, Q76.1–Q78.9, Q79.6–Q79.9 |
| Other non-chromosomal | Q80.0–Q82.4, Q83.0–Q83.1, Q83.8–Q83.9, Q85.0–Q85.9, Q87.0–Q87.8, Q89.0–Q89.9 |
| Specified syndromes (non-chromosomal) | Q87.0–Q87.8 |
| Remainder of other non-chromosomal malformations | Q80.0–Q82.4, Q83.0–Q83.1, Q83.8 – Q83.9, Q85.0–Q85.9, Q89.0–Q89.9 |
| Chromosomal | Q90.0–Q99.9 |
| Downs syndrome | Q90.0–Q90.9 |
| Other chromosomal: Down's | Q91.0–Q99.9 |
| Cranial Neural Crest | Any malformation marked with I above |
| Metabolic and single gene defects | D58.0, D66.0, D67.0, D68.0, D68.1, E23.0., E25.0–E25.9, E70.0, E70.3, E75.0, E76.0, E76.1, E76.2, E84.9, E88.0, E88.9, G10, G11.1, G11.9, G71.0, G71.1, H35.5, Q77.4, Q87.4 |

¹ Cranial-neural crest malformations. ² Tracheo-oesophageal fistula, atresia & stenosis of oesophagus, large intestine, rectum and anal canal.

and single gene defects, in livebirths only, was also formed (Table 2). Minor anomalies were coded, but were excluded from all analyses (Table 3).

Clinical verification of reported conditions in post-Gulf conceptions

Study subjects were asked for details of their own General Practitioner (GP) or armed forces Medical Officer (MO), those of the mother of all reported pregnancies (men), and those of their children. They were also asked for details of the hospital and consultant treating the mother, fetus or child for any serious medical condition reported in

any of the pregnancies or children. Both parents were asked for permission to access medical notes. The signature of the mother was required before any contact could be made with the GP or other medical practitioner regarding a pregnancy ending in a fetal death or other adverse outcome. Among pregnancies conceived after the Gulf war we attempted to obtain clinical confirmation, and information on congenital malformations, for all fetal deaths at 16 weeks or more, or of unknown gestation. In addition, we attempted clinical validation for post-Gulf liveborn children where a congenital abnormality, cancer, other serious childhood medical condition or death was

Table 3: List of minor malformations (exclusions from analyses of congenital malformations)

| |
|---|
| Eye, Ear, Face Neck: |
| Ptosis; Stenosis, stricture, or other malformations of lacrimal apparatus; Ear tag; Other minor and unspecified anomalies of ear |
| Circulatory system: |
| Functional or unspecified cardiac murmur; Absence or hypoplasia of umbilical artery; Single umbilical artery; Patent Ductus Arteriois in liveborn babies with preterm gestation (<37 weeks) or low birthweight (<2500 gm) |
| Digestive system: |
| Tongue-Tie |
| Genital system: |
| Undescended testes; Congenital hydrocele |
| Musculo skeletal system: |
| Clicking hip; Unspecified deformity of hip; Flat feet; Unspecified congenital deformities of feet; Webbed fingers; Webbed toes; Spina bifida occulta |
| Other non-chromosomal malformations: |
| Congenital umbilical hernia; Inguinal hernia; Birthmark; Naevus; Abnormal palmar crease; Skin tags; Other unspecified malformations of skin; Accessory nipple, ectopic nipple, minor anomaly of nipple; Other congenital malformations of integument (hair, nails, etc) |

reported. Pregnancy termination was classified by us as being for non-medical reasons if the pregnancy was unplanned (asked on the questionnaire) and no problems with mother or fetus were reported. We attempted to obtain further clinical details of all terminations not clearly falling into this category. Additional confirmation for all reports of cancer and death was made by requesting a copy of the cancer registration or death certificate, or both, from the NHS central register, linking each child to the register with full name and date and place of birth. At the time of survey (1st August 1998 – 31st March 2001), however, cancer registration details were only reliably available up to 1997. ICD10 codes were changed where appropriate as further details were obtained from clinical notes (or death certificate/cancer registration).

Statistical methods

All analyses in this paper were performed using Stata statistical software [19]. All P-values are two-sided and values less than 0.05 are taken to indicate statistical significance. Proportions were compared using the chi-squared test, or Fisher's exact test where a count of less than 5 was expected in any cell of the table. Means were compared using the t-test, with log transformation if appropriate. All comparisons related to reproductive history were adjusted for age at survey using logistic regression [20].

Results

Characteristics of UK Gulf war veterans

Characteristics of subjects identified for the study are presented in Table 1. Of the 52,811 UK military personnel deployed to the Gulf war, only 2% were women. Average age at deployment was around 27 years for both men and women, the majority being in the Army and in ranks other than officer. At the start of the study only 48% of male and 24% of female GWV were in current service. These figures were slightly higher for NGWV.

Response

Adjusting for undelivered mail, the response (returning a completed questionnaire) among men was 53% for GWV and 42% for NGWV, representing 41% of all men identified for the study (Table 4). The difference in response rates was statistically significant ($P < 0.0001$), as was the difference in proportion with no valid address/mail returned undelivered (11% in GWV and 15% in NGWV, $P < 0.0001$), possibly because GWV were more likely to identify themselves to us in response to publicity campaigns (and, having done so, were then more likely to respond). The 1,290 male GWV reporting post-Gulf conceptions/attempts to conceive who contacted us following publicity campaigns were, however, much more likely to be doing so because of their own symptoms (76% reported one or more new medical problem since the Gulf war) than because of adverse pregnancy outcomes (e.g. 22% reported one or more miscarriage). Furthermore, in terms of reported adverse pregnancy outcome, there was no statistical difference between these GWV and a similar group of 386 NGWV (who had tried for children since January 1991) who also contacted us following publicity for the study – for example, the proportion reporting one or more miscarriage was 19% ($P = 0.16$).

The response among women was considerably higher than that for men, the adjusted rate being 72% for GWV and 60% for NGWV ($p < 0.0001$). This response represents an overall coverage among women of 51%, the marked difference between crude and adjusted response rates (Table 4) reflecting the 21% of questionnaires that either could not be sent because a valid address was never identified, or which were returned undelivered. For both men and women the number of subjects actively refusing to participate was low, around 1%, and did not differ significantly between GWV and NGWV groups. Male GWV were no more likely than NGWV to have ever tried for a child ($P = 0.75$). Among women the proportion reporting

Table 4: Response rates

| | No. | GWV Crude % | Adjusted ¹ % | No. | NGWV Crude % | Adjusted ¹ % |
|---|--------------|----------------|-------------------------|--------------|-----------------|-------------------------|
| MEN | | | | | | |
| TOTAL ELIGIBLE FOR STUDY | 51581 | (100) | - | 51688 | (100) | - |
| Died before start of study, or before receipt or completion of questionnaire ² | 528 | (1) | - | 498 | (1) | - |
| Unable to send (no valid address) ³ | 981 | (2) | - | 1712 | (3) | - |
| Undelivered, returned to sender | 4473 | (9) | - | 6042 | (12) | - |
| TOTAL ASSUMED DELIVERED | 45599 | (88) | (100) | 43436 | (84) | (100) |
| No response | 20936 | (41) | (46) | 24540 | (48) | (57) |
| Refused to participate ⁴ | 284 | (1) | (1) | 457 | (1) | (1) |
| COMPLETED QUESTIONNAIRE⁵ | 24379 | (47) | (53) | 18439 | (36) | (42) |
| Never tried to have children (% of all Completed forms) ⁶ | 5738 | (24) | - | 4187 | (23) | - |
| Children I tried to have children (% of all completed forms) | 18501 | (76) | - | 14176 | (77) | - |
| WOMEN | | | | | | |
| TOTAL ELIGIBLE FOR STUDY | 1230 | (100) | - | 1236 | (100) | - |
| Died before start of study, or before receipt or completion of questionnaire | 7 | (1) | - | 12 | (1) | - |
| Unable to send (no valid address) ³ | 90 | (7) | - | 97 | (8) | - |
| Undelivered, returned to sender | 150 | (12) | - | 185 | (15) | - |
| TOTAL ASSUMED DELIVERED | 983 | (80) | (100) | 942 | (76) | (100) |
| No response | 273 | (22) | (28) | 355 | (29) | (38) |
| Refused to participate | 5 | (0.4) | (1) | 23 | (2) | (2) |
| COMPLETED QUESTIONNAIRE⁷ | 705 | (57) | (72) | 564 | (46) | (60) |
| Never tried to have children (% of all Completed forms) ⁸ | 312 | (44) | - | 242 | (43) | - |
| Children I tried to have children (% of all completed forms) | 390 | (55) | - | 320 | (57) | - |

¹Adjusted for undelivered questionnaires and those not sent, i.e. rate among those assumed to have received a questionnaire. ²Subjects identified to us as dead by a relative or other person at the address of the late subject, or by the MoD in regular updates of deaths to 31st March 2001. Includes 4 subjects (1 Gulf, 3 Era) who were too ill to fill the questionnaire in. ³Includes addresses in Northern Ireland and Eire which had not had been confirmed. ⁴Includes 2 Gulf and 2 Era subjects who subsequently died. ⁵Includes 55 Gulf and 34 Era subjects who died after completing their form. ⁶Includes 140 Gulf and 76 Era subjects where questions about children and pregnancies were left blank on the questionnaire. ⁷Includes 2 Gulf and 1 Era subject who died after completing their form. ⁸Includes 3 Gulf and 2 Era subjects where questions about children and pregnancies were left blank on the questionnaire

conceptions/attempts to conceive was lower, at around 55%, but was again similar in both groups (P = 0.56).

(adjusted response 80% versus 60% among discharged personnel).

The characteristics of respondents are presented in Table 5 (see Additional File 1). Overall, men were more likely to respond if they were older (adjusted response 51% among those aged over 30 at study start versus 42% for those under 30 years), an officer (adjusted response 68% versus 46% among other ranks), and in regular service at the start of the study (adjusted response 58% versus 39% for discharged personnel). Response rates were also slightly higher among those in the RAF (adjusted response 50% versus 48% and 46% for Army and Navy respectively). Women responders appeared representative of all women in the cohort in terms of age but response rates were slightly higher among officers (adjusted response 71% versus 63% for other ranks) and those in regular service

Characteristics of respondents reporting post-Gulf conceptions/attempts to conceive

A total of 18,924 men reported that they had tried for a child since the Gulf war. In this group of men GWV were, on average, 5 months younger than NGWV and were less likely to be officers and in regular service at the time of survey (Table 5 (see Additional File 1)). Their distributions by Service (RN, Army or RAF) were, however, similar. More GWV than NGWV in this group reported that their entire reproductive history had occurred since the Gulf war (72% versus 66%, P < 0.0001), but overall their pregnancy distributions were broadly similar and the average number of reported post-Gulf conceptions was identical in the two groups.

Table 6: Reported pregnancies conceived since the Gulf war¹

| | REPORTED BY MEN | | | | REPORTED BY WOMEN | | | |
|--|-----------------|--------------|--------------|--------------|-------------------|--------------|------------|--------------|
| | GWV | | NGWV | | GWV | | NGWV | |
| | n | (%) | n | (%) | n | (%) | n | (%) |
| TOTAL | 16442 | (100) | 11517 | (100) | 484 | (100) | 377 | (100) |
| Year of conception | | | | | | | | |
| 1990 ¹ | 132 | (1) | - | | 2 | (0.4) | - | |
| 1991 ¹ | 2141 | (13) | 1678 | (15) | 47 | (10) | 28 | (7) |
| 1992 | 2297 | (14) | 1656 | (14) | 61 | (13) | 40 | (11) |
| 1993 | 2436 | (15) | 1729 | (15) | 73 | (15) | 60 | (16) |
| 1994 | 2432 | (15) | 1700 | (15) | 67 | (14) | 58 | (15) |
| 1995 | 2442 | (15) | 1677 | (15) | 82 | (17) | 42 | (11) |
| 1996 | 2467 | (15) | 1711 | (15) | 80 | (17) | 83 | (22) |
| 1997 ² | 2095 | (13) | 1366 | (12) | 72 | (15) | 66 | (18) |
| Multiplicity | | | | | | | | |
| Singleton ³ | 16245 | (99) | 11404 | (99) | 476 | (98) | 373 | (99) |
| Twin | 193 | (1) | 108 | (1) | 8 | (2) | 4 | (1) |
| Triplet | 4 | (0.02) | 5 | (0.04) | 0 | (-) | 0 | (-) |
| Parental pregnancy order⁴ of first pregnancy conceived since the Gulf war: | | | | | | | | |
| Total pregnancies | 10355 | {100%} | 7389 | {100%} | 278 | {100%} | 215 | {100%} |
| 1 | 7558 | {73} | 4894 | {66} | 262 | {94} | 187 | {87} |
| 2 | 1769 | {17} | 1602 | {22} | 16 | {6} | 22 | {10} |
| 3 | 746 | {7} | 634 | {9} | 0 | - | 4 | {2} |
| > = 4 | 282 | {3} | 259 | {4} | 0 | - | 2 | {1} |

¹After first deployment to the Gulf (GWV) or after 1st January 1991 among NGWV or where Gulf deployment dates not known. ²Conceptions after 8th November 1997 (38 weeks before 1st August 1998) excluded. ³All pregnancies under 16 weeks classified as singleton, regardless of number of fetuses or sacs. ⁴Order of pregnancies as reported by the study subject (paternal pregnancy order for men, maternal pregnancy order for women).

Among the total 1,269 female responders, 313 (44%) GWV and 235 (42%) NGWV reported conceptions, or attempts to conceive, after the Gulf war (Table 5 (see Additional File 1)). The two groups were similar in age, but, as with the men, the GWV were less likely to be officers and in regular service at the time of survey. Again like the men, significantly more GWV than NGWV had started their reproduction only after the Gulf war (94% versus 86%, P = 0.002), but again there was no evidence of a difference in the distributions of reported pregnancies after adjusting for age (P = 0.88)

Characteristics of pregnancies conceived since the Gulf war

Male participants reported a total of 27,959 pregnancies conceived since the Gulf war, their distribution by year of conception being remarkably similar between the two groups (Table 6). Women reported a total of 861 post-Gulf pregnancies, the years of conception again being similar among the GWV and NGWV groups (χ^2 test of heterogeneity: P = 0.07). For both men and women the pregnancy order of the first pregnancy conceived since the Gulf (one per subject) was lower in the GWV than NGWV

group (Table 6), reflecting the greater proportion of GWV whose reproductive history started after the Gulf war.

Intensive tracing study

Among ITS-UN, 49% (224) GWV and 47% (216) NGWV remained untraceable (P = 0.67). Adjusted response rates among the remainder were similar in GWV and NGWV at around 27%. Among ITS-NR, 6% GWV and 7% NGWV were untraceable/undelivered at the time of survey (Table 7). A small proportion of non-responders in the main survey might therefore actually never have received the questionnaire. One GWV and 4 NGWV had died. Adjusted response rates were higher among GWV (26% versus 20%) (P < 0.001) but there was no difference in proportions who had tried for children since the Gulf war (50% GWV, 49% NGWV; P = 0.89). The proportions trying for children since the Gulf were, however, higher than equivalent proportions of all main study responders (Tables 5 and 7), which probably reflects the timing of the ITS, around two years after the main study start. Furthermore, among the post-Gulf conceptions reported by ITS-GWV the miscarriage rate was significantly lower than among post-Gulf conceptions reported by main study responders (11% (27 miscarriages / 253 pregnancies) versus 17%

Table 7: Intensive tracing survey – response rates among main study non-responders

| NON-RESPONDER in main study (ITS-NR) | GWV (men only) | | | NGWV (men only) | | |
|---|----------------|--------------|-------------------------|-----------------|--------------|-------------------------|
| | No. | Crude % | Adjusted ¹ % | No. | Crude % | Adjusted ¹ % |
| TOTAL SELECTED FOR STUDY | 1401 | (100) | - | 1530 | (100) | - |
| Dead | 1 | (0.1) | - | 4 | (0.3) | - |
| Unable to trace | 30 | (2) | - | 41 | (3) | - |
| Undelivered, returned to sender | 54 | (4) | - | 68 | (4) | - |
| TOTAL ASSUMED DELIVERED | 1316 | (94) | (100) | 1417 | (93) | (100) |
| No response | 953 | (68) | (72) | 1078 | (70) | (76) |
| Refused to participate ² | 26 | (2) | (2) | 55 | (4) | (4) |
| COMPLETED QUESTIONNAIRE³ | 337 | (24) | (26) | 284 | (19) | (20) |
| REPRODUCTIVE HISTORY AT TIME OF SURVEY among responders: | | | | | | |
| TOTAL | 337 | (100) | | 284 | (100) | |
| Never attempted to conceive | 60 | (18) | | 44 | (15) | |
| > = 1 conceptions/ attempts to conceive since the Gulf war ⁴ | 168 | (50) | | 140 | (49) | |
| REASON⁵ FOR PREVIOUS NON-RESPONSE among subjects returning shortened form of questionnaire (includes refusals): | | | | | | |
| TOTAL | 331 | (100) | | 321 | (100) | |
| Just never got around to it / thought they had sent it back | 151 | (46) | | 117 | (36) | |
| Never tried to have children / all pregnancies before Gulf war | 28 | (8) | | 8 | (3) | |
| All children healthy | 0 | (0) | | 1 | (0.31) | |
| Did not want reminder of "distressing" events | 3 | (0.9%) | | 4 | (1.3%) | |
| Did not serve in the Gulf war / did not have vaccines etc | 3 | (0.9) | | 20 | (6) | |
| Other specific reason for non-response, including "mistrust of MOD" | 43 | (13) | | 30 | (9) | |
| No reason given (usually returned form blank) | 36 | (11) | | 56 | (17) | |
| Did not remember previously being sent a questionnaire | 67 | (20) | | 84 | (26) | |

¹Adjusted for undelivered questionnaires and those not sent, i.e. rate among those assumed to have received a questionnaire, or reached by telephone. ²No subjects reached by telephone refused to participate. ³Response rate 100% for subjects reached by telephone (6 GWV, 14 NGWV among ITS-UN; 23 GWV, 31 NGWV among ITS-NR). ⁴After first deployment to the Gulf (GWV) or after 1st January 1991 among NGWV or where Gulf deployment dates not known. ⁵Subjects were asked to give a reason in free text.

(2,829 miscarriages / 16,442 pregnancies); P = 0.01). For NGWV there was, however, no corresponding difference compared to main study responders (11% (23 miscarriages / 217 pregnancies) versus 13% (1,525 miscarriages / 11,517 pregnancies), P = 0.38).

When asked in the ITS why they had not replied to previous questionnaires, the majority of subjects in both groups gave reasons entirely unrelated to reproduction or Gulf war service: 46% GWV and 36% NGWV either thought they had replied, or said that they had meant to and had simply never got around to it; a further 13% GWV

and 9% NGWV gave specific reasons for non-participation, including mistrust of the MoD; and 20% GWV and 26% NGWV could not remember having previously received a questionnaire (Table 7). 13% GWV (half of whom were refusals) and 9% NGWV (two-thirds of whom were refusals) gave no reason for previous non-participation or current refusal. For the remaining 10% in each group, reasons given for previous non-participation related to lack of relevance for the participant, and reflected the different motivations of the two study cohorts in general: most GWV in this category gave having no children/all pregnancies before the Gulf as the reason (8%);

none of the NGWV in this category had in fact conceived/attempted to conceive since the Gulf war at the time of receiving the previous questionnaire(s), but only 3% gave this as a reason, the majority (6%) giving not going to the Gulf war as the reason for previous non-response. Only 3 GWV and 4 NGWV reported that they did not want a reminder of "distressing events", and a further 2 NGWV (no GWV) reported that they did not consider the study relevant because all their children were healthy.

Clinical verification of reported fetal deaths and malformations

Fetal deaths

We were unable to obtain information from relevant clinical notes for 45 (58%) of the 77 stillbirths reported by GWV and 40 (67%) of the 60 reported by NGWV. This was due either to having no relevant permission from the woman to whom the stillbirth related, no reply being received from the GP or other relevant clinician approached, or because there were insufficient details of the GP/other clinician to allow clinical verification to be attempted. The equivalent figures for miscarriage at ≥ 16 weeks were 107 (61%) for GWV and 95 (75%) for NGWV. Where clinical information was received 91% of the stillbirths and 75% of the miscarriages ≥ 16 weeks reported by GWV were confirmed, compared with 100% of the stillbirths and 84% of the miscarriages reported by NGWV.

Congenital malformations

We were unable to obtain clinical information on 324 (47%) of the 686 pregnancies with one or more malformation reported by male GWV for reasons given in the above paragraph. For male NGWV we were unable to obtain information on 141 (41%) of 342 pregnancies for similar reasons ($p = 0.07$ comparing proportion between GWV and NGWV pregnancies). There was no significant variation in this proportion between the GWV and NGWV pregnancies for any type of malformation (Table 8 (see Additional File 2)). Where we received information from GPs or other relevant clinicians, 330 (91%) of 362 affected pregnancies reported by male GWV had their condition(s) confirmed, compared to 196 (98%) of 201 affected pregnancies reported by male NGWV (Table 8 (see Additional File 2)). Although the malformations reported by females was low, a similar proportion of conditions were able to be validated (53% GWV, 59% NGWV) and all conditions where further information was received were confirmed (Table 8 (see Additional File 2)).

Discussion

This paper describes a large postal survey used to address an issue of topical and public health interest. As in previous studies [13–15] the method was found to be feasible and enabled collection of a considerable amount of infor-

mation on a range of different reproductive outcomes. However the study did have a fairly low response rate and the issue of selection (responder) bias needs to be addressed. Since this is a study of reproductive outcome, selection bias would only impact on the results if it was related to pregnancy outcome. Thus we need to consider if GWV and NGWV were more or less likely than each other to return the questionnaire if they had conceived a pregnancy which ended adversely.

Overall response rates in the survey of non-responders were too low for the reproductive histories of those returning questionnaires to be considered reliably representative of all non-responders in the main study. But the lower miscarriage rate among pregnancies reported by ITS-GWV compared with all GWV responders, a pattern not present for NGWV, is consistent with GWV being more likely to respond to the study if they had experienced a miscarriage. However, other evidence does not argue strongly in favour of a biased response. First, 90% of reasons given by both GWV and NGWV in the ITS for not responding to earlier contacts were unrelated to adverse reproductive outcome, or even to Gulf war exposure, relating more to apathy, or general "mistrust of the MoD". Secondly, the majority of GWV volunteering for the study following publicity were doing so because they were experiencing symptoms themselves, rather than because of adverse pregnancy outcomes. Thirdly, although it might appear that more GWV than NGWV responded to the main survey because they had conceived/attempted to conceive since the Gulf war, among subjects who did report post-Gulf reproductive attempts, the general patterns of reproduction appeared unbiased. That is, the numbers of reported pregnancies, and pregnancy outcomes, were very similar in the two groups. It might be that, compared to NGWV of the same age, Gulf war deployment simply delayed conception of the first pregnancy for GWV. These findings together suggest that selection bias driven by reproductive outcome is not strong in these data. Further discussion of selection bias, plus possible recall bias, will appear in topic-specific papers that follow.

Notwithstanding possible limitations, this study has several advantages. Firstly, we were able to obtain information from discharged personnel as well as those in service at the time of the study. Secondly, we collected information on a range of reproductive outcomes and indicators of offspring health, including congenital malformation in fetal deaths and medical terminations as well as in live-births. Thirdly, the study was large enough to enable malformations to be examined by type. Finally, we were able to obtain verification from clinical notes for over half the congenital malformations reported.

Conclusions

This survey enabled collection of information on a range of reproductive outcomes from veterans of the Gulf war and a suitably matched comparison cohort. The response rate for men was lower than expected but there was little evidence that response was dependent on reproductive outcome in the two groups. These data are now being analysed to determine whether Gulf war veterans and their partners are at increased risk of adverse reproductive events and whether their children have increased risk of serious health problems.

Competing interests

None declared.

Authors' Contributions

NM and PD initiated the research and participated in protocol design, data collection, analysis and writing the paper. GD, SL, MP, SP and PS participated in data collection and analysis. All authors read and approved the final manuscript.

Additional material

Additional file 1

Table 5

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Additional file 2

Table 8

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