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Pregnancy outcomes after paternal radiofrequency field exposure aboard fast patrol boats

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Abbreviations:

CI, confidence interval; EMF, electromagnetic fields; FPB, fast patrol boats; ICNIRP, International Commission on Non-Ionizing Radiation Protection; MBRN, Medical Birth RegisterRegistry of Norway; RF, radiofrequency; RNoN, Royal Norwegian Navy; RR, relative risk; SGA, small for gestational age.

ABSTRACT

Objectives: To investigate adverse reproductive outcomes among male employees in the Royal Norwegian Navy (RNoN) exposed to radiofrequency (RF) electromagnetic fields aboard fast patrol boats (FPB). **Methods:** A cCohort study of RNoN servicemen linked to the Medical Birth RegisterRegistry of Norway, including singleton offspring born between 1967 and 2008 (n=37,920). Exposure during the last three months before conception (acute) and exposure more than three months before conception (non-acute) were analyzed. **Results:** Perinatal mortality and preeclampsia increased after service aboard FPBs during an acute period and also after increased estimated RF exposure during an acute period, compared to service aboard other vessels. Estimated RF exposure during an acute period was associated with perinatal mortality and preeclampsia. No associations were found between non-acute exposure and any of the reproductive outcomes.

Conclusions: Paternal work aboard FPBs during an acute period was associated with perinatal mortality and preeclampsiaadverse reproductive outcomes, but the cause is not clear.

INTRODUCTION

There have been concerns in the Royal Norwegian Navy (RNoN) about the work environment with regard to reproductive health. Based on a cross-sectional questionnaire study of naval employees, a higher risk of congenital anomalies was found in offspring and stillborn babies in a subgroup that had been working aboard a specific fast patrol boat (FPB) that was equipped for electronic warfare.¹ All vessels in the RNoN are equipped with radar, transmitters and antennas. Aboard the smallest ships, like FPBs, the distance between personnel and the antennas is short. Wireless communications equipment such as high frequency antennas and radar is a source of radiofrequency (RF) electromagnetic fields (EMF). Studies of male reproduction and exposure to RF EMF have produced conflicting results.¹⁻³ One reason could be that the assessment of RF exposure in the epidemiological studies is often inadequate.⁴

The aim of the present study was to investigate paternal employment prior to conception aboard vessels in the RNoN and the risk of adverse reproductive health outcomes, in particular among servicemen exposed to RF EMF. Transmitting patterns and RF exposure measurements aboard the fast patrol boats have been described in detail in a previous paper,⁵ and form the basis for calculating an RF exposure matrix. A register cohort study was designed, whereby the complete cohort of naval servicemen was linked to the Medical Birth RegisterRegistry of Norway (MBRN) to obtain information about all pregnancies and offspring. Adverse pregnancy outcome were studied. Occupational exposure during the last three months prior to conception and exposure more than three months before conception were analyzed separately because of possible differences in biological mechanisms.

MATERIAL AND METHOD

The RNoN military personnel cohort comprises complete data for all officers and enlisted personnel from January 1, 1950 until 2004.⁶ It contains work history data, including all positions, workplaces, and work periods for each employee. In this article, only male personnel were included: 28,337 servicemen with 264,065 specified periods of service, both aboard vessels and land-based. The cohort of servicemen was linked to the Medical Birth RegisterRegistry of Norway to obtain information about all pregnancies and offspring from 1967 to 2008.

Acute and non-acute exposure

Exposure during a three-month period prior to conception was deemed to cover the period from the start of sperm cell production until the sperm cells reach full maturity. This exposure was defined as acute exposure, with a possible effect on the sperm cells.⁷ Any exposure more than three months prior to conception was deemed to be non-acute exposure, with possible effects on testicular stem cells or DNA.

For some pregnancies, the father's service involved both acute and non-acute exposure. First we analyzed the data for non-acute exposure by excluding those with acute exposure. Thereafter, acute exposure was analyzed regardless of non-acute exposure. Additional analyses were performed for acute exposure alone if significant effects were found of acute and non-acute exposure.

Exposure classifications

Three exposure classifications were used for both acute and non-acute exposure (Figure 1).

a) Related to work aboard vessels. We analyzed the effect of acute and non-acute exposure aboard all vessels, using land-based personnel as a reference group.

b) Related to work aboard FPBs. The effect of acute and non-acute exposure aboard FPBs was compared to work during corresponding periods aboard other vessels, excluding FPBs.

c) Related to RF dose assessment aboard FPBs.

The third classification was based on calculated individual RF exposure doses aboard FPBs. There were few acute exposed (n=660), and the distribution contained clusters in which the largest cluster (30% of the exposed) had a slightly higher value than the median exposure dose. Dividing acute exposure dose into two or three equally-sized groups could lead to misclassification of the exposure. The acute RF exposure dose group was therefore divided into three groups (according to the rule of ten:⁸ low (below 1.0), medium (1 – 9.9), and high (above 10). This was also done in order to contrast the lowest and highest exposure groups.

The distribution of calculated dose was positively skewed for non-acute exposure, with relatively few pregnancies after a very high paternal exposure dose. The non-acute RF exposure dose group was divided into three equally large groups: low (≤ 3.8), medium (3.8 – 9.5) and high (> 9.5) after exclusion of pregnancies resulting in congenital malformations or perinatal deaths. In all analyses of RF exposure, we used the same reference groups as for work aboard FPBs.

RF exposure on fast patrol boats

The RNoN fleet comprises different vessels that are equipped with radar, transmitters and antennas. The vessels include small FPBs, where the distance between personnel and the transmitting equipment is short. Each FPB has high frequency (HF) antennas. The frequency band 2.1 - 4 MHz was used, with a maximum output power of 250 W, although it was mostly used in the 10-50 W range. In 1994, an additional HF antenna was installed aboard the FPBs. Each boat also had two radars, one 9.4 GHz for navigation and one 9.1 GHz for weapon

control, both with 25 kW peak power. Since 1950, there have been different classes of FPBs with similar kinds of hulls and transmitting equipment.⁵ In two FPB classes, Snøgg and Hauk, the officers' mess and the captain's cabin were above deck.

Stationary measurements were carried out by the RNoN of electric fields emanating from the antennas and radars aboard the FPBs (in 1998 and 2005). The measurements of magnetic fields were not complete and they were not included in the further calculations.⁵ The measurements were carried out in spots where the crew was most likely to be located. The spots were grouped into five locations: the upper bridge, bridge, aft deck, officers' mess and below deck. Details concerning the measurements, transmitting patterns and different approaches to calculating total RF exposure were published recently.⁵ In the current study, we used exposure calculations based on squared percentages of ICNIRP guideline limits⁹ ("squared ICNIRP percentage"). The contribution from the different equipment was calculated by averaging the field strength weighted for each frequency in accordance with ICNIRP⁹ and then averaging the squared ratios for the different spots. Finally, the total average RF exposure level was calculated for each location by adding together the contribution from all the equipment.⁵

Job group

Based on interviews of naval employees with specific knowledge of the normal working positions of the crew, all service aboard FPBs was classified into three job groups according to the time spent (as a percentage) in the five locations (Table 1). Group I largely consisted of artillerymen and personnel (not officers) who operated weapons such as torpedoes and cannons. Group II typically included bridge officers and radar operators. Group III included jobs below deck, such as engine room personnel and telegraph/radio operators.

Individual RF exposure dose

The FPBs sailed approximately 70% of the time and were moored at quay 30% of the time. The radars were switched off when the vessels were moored. The time servicemen spent in different locations differs between sailing periods and periods when the boat was moored (Table 1). Taking this into consideration, the job group average RF exposure level based on the squared ICNIRP percentage was calculated by multiplying the percentage of time the group spent in a specific location (Table 1) by the average RF exposure level for the location,⁵ and, finally, by adding together the five locations. Calculations were done for each job group, time period and FPB class. This resulted in a squared percentage of the ICNIRP guideline limits (Table 2).

The individual RF exposure dose was estimated by multiplying the average RF exposure level by the number of days of service in the job group, time period and FPB class in question. This resulted in a unitless quantity. The number of days of service was obtained from the RNoN cohort.

Medical Birth RegisterRegistry of Norway

The Medical Birth RegisterRegistry of Norway (MBRN) is based on compulsory notification of all live births and stillbirths from 16 weeks of gestation (12 weeks from 2001) since 1967. In a standardized notification form, data on demographic variables, maternal health before and during pregnancy, complications during pregnancy, delivery and pregnancy outcome are reported by the attending midwife and/or the physician present.

Study pregnancies

By means of the mother and father's personal ID numbers, pregnancies involving parents in the RNoN were identified. The birth month and year were obtained and the conception date

was calculated by subtracting the gestational age from the 15th of the birth month. Gestational age was based on the prenatal ultrasound scan date, and, if missing, it was calculated on the basis of the last menstruation. Gestational age was missing in 4% of the pregnancies and birth weight was therefore used to estimate gestational age when calculating the conception date.¹⁰ The study population was restricted to singleton pregnancies involving servicemen employed in the RNoN prior to conception. A total of 287 pregnancies were excluded due to the mother's service in the RNoN before birth. Seventy-two pregnancies with a gestational age of less than 22 weeks or a birth weight of less than 500 g were excluded due to uncertainties concerning registration. For each pregnancy, information was obtained about the year of birth, the mother and father's age, and parity. Due to insufficiently specific job titles, 1,129 pregnancies were set to missing in the analyses of RF exposure dose.

Reproductive outcomes

Congenital malformations are diagnosed during the medical examination of newborns at the birth clinic and reported to the MBRN. Since 1999, the RegisterRegistry also receives notification from neonatal wards. Congenital malformations included all malformations based on the International Classification of Diseases. No specific malformations were analyzed separately. Perinatal mortality was defined as stillbirth and death within the first week of life.

The sex ratio was measured as the ratio between the number of boys and the numbers of girls. Low birth weight was defined as a birth weight of less than 2500 g (missing for 34 pregnancies). Preterm birth was defined as a gestational age of less than 37 completed weeks. To exclude obvious misclassifications of preterm birth, preterm pregnancies with a gestational age-specific birth weight z-score greater than 3.5¹⁰ were excluded (n=67). Furthermore, 1,532 pregnancies had missing data for gestational age. Small for gestational age (SGA) was defined as a birth weight of less than the tenth percentile for gestational age,¹⁰ and 1,570

pregnancies were set to missing due to unknown gestational age or birth weight. The definition of pregnancies with preeclampsia was in accordance with the MBRN's definition.¹¹

Statistical analysis

Descriptive statistics for paternal and maternal age, parity, days of service, and individual RF exposure dose by exposure classification were provided for acute and non-acute exposure.

Pearson bivariate correlations were used to quantify the associations between days of exposure and exposure dose.

The calculated acute exposure dose had clusters in the distribution. Thirty percent of the distribution had a slightly higher value (2.07) than the median exposure dose (2.047). The acute exposure dose was divided according to the rule of ten.⁸ This was done both to reduce the possibility of misclassification and to contrast the lowest and highest acute exposure groups.

Log-binomial regression was used to estimate relative risks (RR) and 95% confidence intervals (CI) for adverse reproductive health outcome. Due to a change in registration procedures, analyses of congenital malformations were adjusted for year of birth before and after 1999 in a log-binomial regression analysis. The risk of preeclampsia during first pregnancy is approximately twice as high as in later pregnancies,¹² so the estimated RR for preeclampsia was adjusted for parity in two groups (first pregnancy; second or later pregnancy) in a log-binomial regression. All analyses performed were adjusted for year of birth and maternal and paternal age as continuous variables. Tests for linear trend between the calculated RF exposure dose and perinatal death and preeclampsia the pregnancy outcome variables that were significant in the log-binomial regression model were performed using Mantel-Haenszel chi-square linear by linear analysis. Statistical significance level was set to 0.05. The data were analyzed using SPSS 15.0 (SPSS Inc., Chicago, Illinois).

RESULTS

A total of 37,920 pregnancies were included in the study, in 18,360 of which the fathers had land-based service only (Figure 1). The number of pregnancies involving servicemen with a pre-conception non-acute RF exposure dose was 6604,456, while the number involving non-acute exposure was 4,456 660.

The mean age of fathers with land-based service and with service in a non-acute period was similar, while those who had been subjected to acute exposure were younger. The same pattern was seen as regards the mother's age (Table 3). The percentage of first born among men who had served during an acute period was higher than among those who served during a non-acute period.

The mean number of days of service during a non-acute period aboard vessels was 710, while the mean number of days aboard FPBs was 509 (Table 3). The distribution of RF exposure dose was positively skewed for non-acute exposure, with relatively few pregnancies after a very high paternal exposure dose (Table 3). The correlation between exposure dose and days of exposure was 0.11 for acute exposure and 0.47 for non-acute.

For service during both an acute and non-acute period, there was an increased relative risk of low birth weight among the offspring of fathers who had served aboard vessels compared to those with land-based service only (Table 4). Analyzing acute exposure alone, the adjusted RR for low birth weight was 1.19 (95% CI, 0.45 to 3.14). A small increased relative risk was found of SGA among the offspring of fathers who had served aboard vessels during a non-acute period (Table 4).

An increased relative risk was found of perinatal mortality and pregnancies complicated by preeclampsia after paternal work aboard FPBs during an acute period compared to service aboard other vessels (Table 4). None of the perinatal deaths resulted from preeclamptic

pregnancies. The adjusted RRs for perinatal mortality were 1.82 (95% CI, 0.54 to 6.13) and 2.87 (95% CI, 1.25 to 6.59) , respectively, in the *low* and *medium* RF-exposed groups aboard FPBs compared to service aboard other vessels. In the *high* exposed group, there were no perinatal deaths among the 14 pregnancies (Table 4). The adjusted RR for preeclampsia was 2.67 (95% CI, 1.50 to 4.75) in the *low* RF exposure dose group compared to the reference group. No increased risk was found for a *medium* exposure dose, while, for a *high* exposure dose, the RR was 6.07 (95% CI, 1.77 to 20.8) (Table 4). There were only 14 pregnancies in the high exposure group, two of which were complicated by preeclampsia. Testing for linear trend showed significant increased risk with higher doses for both outcomes: perinatal death P=0.01 and preeclampsia P=0.03. Since the measurements were carried out in 1998 and 2005, while we used service periods dating back to 1950, based on the assumption that exposure would be the same over time, we carried out the same analysis for births during the period 1995 to 2008 regarding acute exposure. The analyses showed similar results.

Non-acute RF exposure or service aboard FPBs was not associated with any of the adverse reproductive outcomes when compared to service aboard other vessels (Table 4).

Four percent of the pregnancies had a calculated conception date based on birth weight because of missing data for gestational age. Analyzing the data after excluding missing gestational age reduced the risk estimates slightly.

DISCUSSION

This study reveals an increased risk of perinatal mortality and pregnancies complicated by preeclampsia after paternal service aboard FPBs during a three-month pre-conception period compared to work aboard other vessels. The same was seen among servicemen with an estimated RF exposure dose aboard FPBs, but there was no clear dose response relationship. A calculated RF exposure dose or service aboard FPBs more than three months before

conception was not associated with any adverse reproductive outcome compared to work aboard other vessels.

Work aboard FPBs was assumed to be related to RF exposure to a greater extent than work aboard other vessels because of the short distance to the RF-emitting equipment. An RF exposure dose was used to improve exposure characterizations. There were few pregnancies involving paternal exposure in the *high* exposed group, and this group also represents a high daily average RF exposure level. The distribution of the calculated non-acute exposure dose was positively skewed, with relatively few pregnancies after very high paternal exposure. The doses were nevertheless grouped into three groups of equal size. Land-based service was used as a reference group. There was no information on RF exposure in this group, but it is unlikely that they had worked near RF equipment. They mainly worked in administrative positions performing office work.

We found an association between service aboard FPBs during an acute period and perinatal mortality. There was no clear dose response relationship with RF exposure even though there was a significant linear trend. The *medium* exposed group had a higher RR than the *low* exposed group, while there were no perinatal deaths in the group of *high* RF-exposed fathers, which only counted fourteen pregnancies. Other studies of paternal RF exposure and perinatal death are equivocal. Two studies did not find any association with paternal occupation involving probable RF exposure.^{2,13} A cross-sectional questionnaire study in the RNoN found a higher risk after work aboard a specific fast patrol boat used for electronic warfare,¹ but the causality was unclear. These studies used rough exposure characterization and did not discriminate between non-acute and acute exposure periods.

Paternal service aboard FPBs during an acute period was associated with an increased risk of partners experiencing pregnancies complicated by preeclampsia. A high risk was also found for the *low* and *high* average RF exposure dose group during the acute period. There

were few pregnancies involving the *high* exposed group and, consequently, the result was not robust. In the *high* RF exposure dose group, no offspring with SGA and preeclampsia were identified. Preeclampsia is a serious placenta disorder, affecting both mother and child. The pathogenesis is incompletely understood,¹⁴ and both mother and fetus (via the father) may contribute to the risk.¹² To our knowledge, no published studies have studied paternal RF exposure and pregnancy-related conditions, although fathers' environmental exposure has been discussed.^{15,16}

There were no associations between acute RF exposure or work aboard FPBs and sex ratio, congenital malformations, low birth weight, SGA or preterm birth. Non-acute exposure aboard an FPB was not associated with any of the pregnancy outcomes in this study. This is in line with most previous studies; acute and non-acute paternal RF exposure among physiotherapists was analyzed, but no significant increased risk of birth defects was found,¹⁷ and a paternal occupation with probable exposure to RF was not associated with congenital malformations.^{2,13} In a case control study of Down syndrome, paternal work with radar was found to be related to the syndrome.¹⁸ This was not confirmed, however, in a re-examination of the data together with additional pairs of cases and controls.¹⁹ Work on a specific FPB was found to be related to congenital malformations, but the causality was unclear.¹ Conflicting results have also been published regarding RF exposure and preterm births^{2,13} and sex ratio.^{2,3}

RF electromagnetic exposure can have both thermal and non-thermal effects. It is unlikely that low-level exposure to RF as seen in our study has enough energy to cause heating.²⁰ However, biological effects can also occur in which RF heating is neither an adequate nor a possible mechanism.²¹ Animal studies and *in vitro* studies have shown genetic effects after RF exposure, but the results vary²⁰ and have not been confirmed in human studies. It has been suggested²² that there are several thermoreceptor molecules in cells, and that they also at lower temperatures than when the ordinary thermic effects are registered, activate a cascade

of second and third messenger systems, gene expression mechanisms and production of heat shock proteins in order to defend the cell against metabolic cell stress caused by heat. Other researchers believe that an increase in stress proteins are unrelated to thermal effects, since they occur for both extremely low frequencies (ELF) and radio frequencies (RF), which have very different energy levels.²³ Non-thermal effects on cell membranes²⁴ have been suggested, as well as changes in melatonin levels and/or DNA damage in the genital tract²⁵ due to RF EMF. A recent study concluded that exposure to radiofrequency signal waves within parts of the brain close to the cell phone antenna resulted in increased levels of glucose metabolism, but the clinical significance of this finding is unknown.²⁶ Based on an *in vitro* study, Agarwal et al.²⁷ found that RF exposure from mobile phones can lead to oxidative stress in human semen. No evidence has been found for the mechanism involved, however. The biological mechanisms behind non-acute and acute effectsexposure could be different. We were able to analyze these effectsexposure separately and found only acute effects after acute exposure, which could indicate that a possible association between paternal occupational RF exposure and adverse reproductive outcome is reversible.

The increased risk found for perinatal mortality and preeclampsia could be due to confounding factors. We compared service aboard FPBs with service aboard other vessels to control for being away from home, lifestyle factors, stress, and unfavorable work hours. These issues could differ between different types of vessels, however. Unlike the other vessels, the FPBs also involved exposure to diesel exhaust, both through proximity to the exhaust system and because the FPBs operated in squadrons and were moored close together.²⁸ There could also have been more vibration aboard FPBs than on other vessels.²⁹

An increased risk of low birth weight and SGA was found among the offspring of servicemen with non-acute service aboard vessels compared to land-based service. This seems to be related to service aboard vessels and not to RF exposure, since there was no further

increased risk in the subgroup who had served aboard FPBs. These findings are in line with a recent study. Based on 29 SGA births where the fathers worked as seafarers, an odds ratio of 1.08 (95% CI: 0.75 to 1.55) compared to the total study population was found; the number of seafarers was not stated.³⁰ Work environment factors and lifestyle aboard navy vessels could be associated with adverse reproductive outcome, and this must be considered. Factors such as tobacco smoking and alcohol³¹ have adverse effects on semen quality. These factors could differ for service aboard vessels and land-based service. Several studies have shown high consumption of alcohol and tobacco among naval personnel.^{32,33} Paternal occupational exposure to lead was associated with both preterm birth and low birth weight in a review article.³⁴ We have no information about lead exposure in our study, but lead has been present during the handling of ammunition on board vessels. This could be associated with lead exposure.³⁵

This study has several strengths; it is based on the complete RNoN personnel cohort.⁶ The cohort was linked with compulsory notifications of all births in Norway and was thus free of response bias. Exposure assessment and time of exposure are often weak in epidemiological studies of RF exposure. In the current study, it was possible to distinguish between non-acute and non-acute exposure prior to conception.

The acute exposure dose was divided into three groups, with large contrasts between low and high exposure. Misclassification problems were probably reduced at the expense of small groups. Sensitivity analyses of biases³⁶ were carried out to assess the impact of misclassification on the results, however. For possible misclassification of perinatal mortality between none exposed and medium exposed, the calculations shows RR between 2.5 and 3.7 for different values of sensitivity and specificity (1.0, 0.975, 0.95, 0.9). The unadjusted RR for perinatal mortality was 3.2 in the medium acute RF-exposed groups compared to reference group.

The non-acute exposure was so skewed that it was difficult to use it as a continuous variable, and it was divided into three equal groups since there was no natural cluster or other information indicating where to set the cut-off. Grouping on the basis a continuous exposure variable can introduce misclassification. In this situation, it would represent a non-differential misclassification and could bias possible associations towards null.

The individual RF exposure dose was based on stationary measurements performed by the navy in 1998 and 2005. It varied greatly⁵ and must therefore be interpreted with caution. RF exposures were only based on electrical fields, not magnetic fields, and they are lower than the actual exposure. The relative differences in our cohort would probably not differ, however. It must be underlined that the measured levels were low compared to other workplaces.³⁷ We assumed the same RF exposure over time, but it could have differed. Nevertheless, adjusting for year of birth or limiting analyses to births during the last fourteen years among the acute exposed did not affect the estimates. Non-acute individual RF exposure dose correlated better with days of exposure than acute exposure. Since the correlation was as low as 0.11 for acute exposure, the average daily exposure level seems to have been the dominant factor in relation to the individual acute exposure dose. Due to lack of information about possible mechanisms affecting reproductive health, we chose an accumulated dose over the relevant period. The dose took into account the possibility that an effect would increase with the number of days of exposure as well as with a higher exposure level.

Compared to the general birth cohort in Norway, our data suggest a reduced prevalence of adverse reproductive outcomes. A possible cause is related to the registration procedures of the MBRN. Most fathers of live-born children are automatically registered, but in cases of stillbirths, registration of the father is not compulsory. Consequently, among registered fathers, the occurrence of stillbirths will be lower than for the total birth cohort, and stillbirth in general is associated with most of the other outcomes. It is unlikely that the registration of

fathers would differ between the unexposed and exposed groups and cause biased results. The registration of congenital malformations before 1999 has low ascertainment, but, again, there is no reason to believe that it varies between the unexposed and exposed groups in this study.

It is possible that multiple testing in this study has given rise to significant findings. We performed corresponding log-binomial regression analyses with 99% CI. The remaining significant results were increased risk of preeclampsia after low and high acute RF exposure (99% CI: 1.25-5.69 and 1.20-30.6, respectively) and increased risk of low birth weight after work aboard vessels both in an acute and non-acute period (99% CI: 1.01-1.65 and 1.04-1.39, respectively). This weakens the results regarding perinatal mortality. We cannot rule out conditions other than RF exposure aboard FPBs as the cause of the significant associations. However, since work aboard FPBs was compared to service aboard other vessels, lifestyle factors and working conditions associated with seafarers are unlikely to be of importance.

In conclusion, we found that paternal work aboard FPBs during the three last months before conception was associated with an increased risk of perinatal mortality and pregnancies complicated by preeclampsia. The cause is unknown but however, this study showed a weak but based on the finding of a significant linear trend, and based on this we cannot rule out an RF effect. However, this needs to be confirmed by further studies focusing on exposure characterization as well as exposure in relation to time of conception. There were no associations between acute RF exposure and sex ratio, congenital malformations, low birth weight, preterm birth or SGA. Occupational exposure to RF fields aboard FPBs in the RNoN prior to three months before conception was not associated with adverse reproductive outcomes.

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Legend to figure 1:

Figure 1. Number of pregnancies (n = 37,920) by paternal service related to exposure classification by non-acute (exposure in periods more than three months before conception) and acute exposure (exposure during the last three months before conception), the RNoN cohort linked with MBRN (1967-2008).