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## Shift work and reproductive health

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Nonstandard workhours may disturb normal body functions, but their relation to reproductive outcome is poorly understood. Two newly published studies suggest an association between rotating shift work and prolonged waiting time to pregnancy. Seven of nine studies on spontaneous abortion suggest that some forms of shift work may be associated with increased risk. Four studies indicate that shift work including night schedules may be related to preterm birth. Moreover, some results have related rotating schedules to intrauterine growth retardation. In the published studies, the type of work schedule examined has varied, and the applied definition of shift work has not necessarily been clear. The main interest areas, however, have been work involving evening and night shifts, rotating or changing schedules, and the irregularity of work patterns. Although the evidence is not ample and remains ambiguous, it is prudent to consider shift work as a potential risk to reproduction.

**Key terms** birthweight, fecundity, female exposure, menstrual disorders, pregnancy, preterm birth, spontaneous abortion, time to pregnancy.

Nonstandard workhours may disturb normal body functions (1). For example, employees in rotating shift work must adapt each time that their schedule changes, and many physiological functions and systems that are circadian in nature can be disturbed. However, the relation to reproductive outcome is poorly understood. Hormonal disturbances, either as a direct effect of changes in the circadian rhythm or indirectly through psychosocial stress and disturbed sleep, are the factors most often suggested (2). Early fetal loss, preterm birth, and lowered birthweight have received the most attention in connection with shift work (3). Recently, problems with fecundity have increasingly been used as biological indicators of occupational effects on reproduction.

This paper presents a review of the epidemiologic studies on the reproductive hazards of women's shift work. The identification of relevant publications was done stepwise. The references prior to 1989 were collected without literature data bases being consulted (4). In the summer of 1994, MEDLINE, NIOSHTIC, CISDOC, HSELINE, and EMED were searched for articles published since 1989 (3). The key words "shift work" or "work schedule" were combined with the following terms or their synonyms: reproduction, pregnancy, hormonal disturbance, menstruation, fecundity, infertility, abortion, birth defect, birthweight, and gestational age.

Complementary searches were performed in late 1995 (for 1994 and 1995) and in late 1996 (for 1995 and 1996). The main results of the identified epidemiologic studies are reviewed. For menstrual disorders, only irregularity of the menstrual cycle has been included (eg, results on dysmenorrhea were excluded). Moreover, individual results on pregnancy complications (eg, vaginal bleeding) and published negative results on selected birth defects (4) have not been reviewed.

### *Time to pregnancy*

According to a Swedish study, midwives doing rotating 2-shift or 3-shift work and those working only nights had reduced fertility as compared with midwives working regularly in the daytime (5). All the women who were born in 1940 or later and who, in 1989, were found in the membership files of the Swedish Midwives' Association comprised the target population of the study. The measure of fertility was the time to pregnancy, that is, the number of menstrual cycles required to become pregnant. A postal questionnaire was sent to all eligible midwives in Sweden for data on their time to pregnancy and their work conditions during the period related to the

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most recent, planned pregnancy that had terminated after 1983. Time to pregnancy provides an estimate of per cycle probability of becoming pregnant, and it was calculated for each work schedule category, and its relation to daytime work was expressed as a fecundability ratio. Each woman was allowed to contribute a maximum of 13 cycles to avoid interference from medical treatment for infertility. The adjusted fecundability ratios for 2-shift, 3-shift, and night work were 0.78 [95% confidence interval (95% CI) 0.65—0.94], 0.77 (95% CI 0.61—0.98), and 0.82 (95% CI 0.65—1.04), respectively.

The data from a European multicenter study were in favor of an association between changing or rotating shift work and prolonged waiting time to pregnancy (6). In the pregnancy-based survey of this European project, the pregnant women encountered during a prenatal visit or women who had given birth at a hospital or a clinic were consecutively enrolled between February 1992 and December 1992. They represented pregnant or delivering women from well-defined geographic areas of Denmark, France, Germany, Italy, and Sweden. The information, collected with self-administered questionnaires or by interviewers, pertained to the current or just-ended pregnancy, including time to pregnancy, occupational and other exposures at the beginning of the waiting time, and help-seeking because of inability to conceive. In the analyses, 9.5 months was used as the cutoff point of the waiting time to identify subfecundity. The adjusted odds ratio of subfecundity was 2.0 (95% CI 1.4—2.8) for changing or rotating shift work as compared with daytime, evening, or night work.

In a recently published study, all women who delivered a live child in the preceding week of the interviews during a period of 2 months in 1993 in 4 hospitals (in Bergamo, Milan, Rome, and Terni) were included (7). In the group of women who had done shift work, the crude percentage of women conceiving after 12 months was 17.9, and in the nonshift group the corresponding percentage was 10.5. However, this difference was markedly reduced when confounding variables were controlled in the analysis. The adjusted conception (fecundability) rate ratio for shift work was 0.9 (95% CI 0.7—1.2).

Shift work was included as a factor of potential interest in an earlier Danish population-based survey that focused on life-style factors and fecundity (8). All pregnant women in 2 cities (Odense and Aalborg) were given a questionnaire in the last trimester of their pregnancy between 1984 and 1987. Subfecundity was defined as a waiting time of 1 year from the cessation of contraception to the achievement of pregnancy. Shift work had no effect on subfecundity; the adjusted odds ratio was 0.9 (95% CI 0.7—1.0) for shift work as compared with no shift work.

In 1981, in Japan, a questionnaire on work conditions and health was distributed to workers belonging to 33

labor unions. The crude rate of pregnancy was lower for the women doing shift work including night work (10.0%) than for the women doing daytime work (18.1%,  $P < 0.01$ ) during the 2 years preceding the study (9). The shift workers were nurses or telephone operators. The reference group of day workers was more heterogeneous, including women with various jobs.

### ***Irregular menstrual cycle***

Published study results on irregular menstrual cycles are scant. In a Japanese study on night and shift work (9), the women doing night shifts had a higher crude rate of irregular cycles than did the daytime workers (36% versus 28%,  $P < 0.01$ ). Ten years later, another Japanese study reported similar results concerning night work as compared with daytime work in a population including teachers, office workers, nurses, factory workers, and barmaids (10). In a third study in 1987—1988, a medical examination and questionnaire were administered to workers in 17 poultry slaughterhouses and 6 canning factories in western France (11). Workers with irregularly varying work schedules (varying beginning, ending, or hours per week) not including night shifts had elevated crude rates of irregular menstrual cycles. In the final analysis, the adjusted odds ratio for work with a varying beginning of the workday was 2.0 (95% CI 1.2—3.6) in a comparison with work on a 2-shift schedule changing from the morning to the afternoon shift regularly on a weekly basis.

### ***Spontaneous abortion***

Nine studies have been published on shift work and fetal loss (table 1). The most recent is the Swedish study conducted among midwives in which reduced fertility was associated with nonstandard workhours (12). The results indicate that night work and 3-shift schedules may be associated with an increased risk of spontaneous abortion. The odds ratio was 1.63 (95% CI 0.95—2.80) for night work as compared with daytime work, and for 3-shift work the corresponding odds ratio was 1.49 (95% CI 0.86—2.59). The increase in the risk related to night work was found mainly for late spontaneous abortion (table 1).

In addition, 6 of the available 9 studies on nonstandard workhours and fetal loss reported an elevated risk of spontaneous abortion (9, 13—17). Night work seemed to be hazardous in 2 studies (9, 17), but in 2 others (15, 18) no elevated risk was observed when night work was analyzed explicitly. [In reference 15, the adjusted rate ratio for regular night work was 0.9 (95% CI 0.5—1.8).]

**Table 1.** Studies on shift work during pregnancy and spontaneous abortion. (OR = odds ratio, 95% CI = 95% confidence interval, RR = rate ratio, O/E = ratio of observed to expected)

Location	Exposure	Definition of outcome	Observed effect
Japan (9)	Shift work including night work, according to a retrospective questionnaire administered in 1981	Spontaneous abortion within the past 2 years, reported in the questionnaire	Night work compared with day work associated with higher rate (36% versus 18%, $P < 0.05$ )
Sweden (12)	Always night, 2-shift, or 3-shift work as a midwife for more than half of the time during the first trimester of pregnancy between 1980 and 1989, according to a postal questionnaire	Spontaneous abortion reported in the questionnaire if the woman stated that it had been diagnosed by a physician or had been preceded by a positive pregnancy test	Spontaneous abortion after the 12th week of gestation, associated with night work (adjusted OR 3.3, 95% CI 1.1-9.9) in a comparison with day work
Göteborg, Sweden (13)	Shift work during the first trimester of pregnancy in university laboratories from 1968 to 1979, according to a postal questionnaire	Spontaneous abortion, reported in the questionnaire and verified in hospital records	Elevated rate compared with mothers not in shift work (age adjusted RR 3.2, 95% CI 1.4-7.5)
Finland (14)	Work arrangements other than normal daily work in selected departments of general hospitals, according to a postal questionnaire sent to the leading head nurses of the hospitals	Spontaneous abortion between 1973 and 1979, determined from the Finnish Hospital Discharge Register and information on polyclinic cases	Elevated OR for rotating 3-shift work compared with day shift or rotating 2-shift work (adjusted OR 1.5, 95% CI 0.9-2.5)
Mölnådal, Sweden (15)	Irregular and inconvenient work schedules at a hospital between 1980 and 1984, according to a postal questionnaire	Spontaneous abortion reported in the questionnaire and verified in hospital records	Elevated rates for irregular workhours and rotating 3-shift work compared with work during the day only (adjusted RR 1.4, 95% CI 0.8-2.5, and 1.5, 95% CI 0.6-4.1, respectively)
Montreal, Canada (16)	Employment of $\geq 30$ hours a week doing changing shift work at conception, as reported retrospectively by the mother in an interview	Spontaneous abortion in previous pregnancies of women interviewed after recently completed pregnancies between 1984 and 1985	Elevated O/E (overall O/E 1.3, $P < 0.01$ )
Calgary, Canada (27)	Work for pay from 3 months preceding to 4 months after the last menstrual period and shift work schedules based on interview data	Spontaneous abortion, determined by data from 3 hospitals between 1984 and 1985	Effect of shift work nonsignificant in a comparison with nonshift work, when analyzed in several ways
Montreal, Canada (17)	Four types of work schedules, based on interview data	Pregnancy loss (spontaneous abortion or stillbirth), determined by 1 hospital between 1987 and 1989	Elevated OR for fixed evening schedule (adjusted OR 4.2, 95% CI 2.2-7.9) and fixed night schedule (adjusted OR 2.7, 95% CI 0.5-13.4) in a comparison with fixed day schedule
Santa Clara, CA, United States (18)	Evening/night work or variable types of shift schedule, based on interview data	Spontaneous abortion for which a pathology specimen was analyzed between 1986 and 1987 after pregnancies of women residing in Santa Clara	No increased OR values for evening or night work (adjusted OR 0.8, 95% CI 0.5-1.2) or variable shift schedules (adjusted OR 0.6, 95% CI 0.4-1.0) in a comparison with day work

In 3 of the 6 positive studies, spontaneous abortion was related to some form of rotating schedule (14–16).

### **Preterm birth and birthweight**

Preterm birth is a pregnancy complication that has been examined in relation to shift work in 5 studies (table 2). The most recent of these studies was conducted in Canada (19). In it, the increased risk of preterm birth associated with regular evening or night work appeared to be confined to women who had continued working after 23 weeks of pregnancy. The adjusted odds of giving birth before 37 completed weeks of gestation was 2 times higher than for women who did day work only or shift work and who stopped working 3 weeks before the 3rd trimester. The corresponding odds ratio for women who had been exposed to regular evening or night work but had

stopped working before 24 weeks of pregnancy was 1.1 (95% CI 0.5–2.8), and, for the group that had done day work only or shift work after 23 weeks of pregnancy, it was also 1.1 (95% CI 0.8–1.6).

Previous published results on preterm birth do not permit an evaluation of the specific effect of regular evening or night work (table 2). The early French study by Mamelle and her colleagues on preterm birth focused on sources of fatigue in the job (20). Shift work was not an element of the composite score of fatigue that correlated with preterm birth in the study data. Instead, a higher crude rate of preterm birth for shift and night work was reported separately (table 2). However, another French study found no association between preterm delivery and night work, at least partly during the first 2 trimesters (21). In a large pregnancy study in Montreal, changing shift work was related to preterm birth, but not consistently (22). A recent Chinese study showed an association between rotating shift work and preterm birth

**Table 2.** Studies on shift work during pregnancy and preterm birth. (OR = odds ratio, 95% CI = 95% confidence interval, RR = rate ratio, O/E = ratio of observed to expected, NS = not significant)

Location	Exposure	Definition of outcome	Observed effect
Quebec City, Canada (19)	Evening/night only or shift work, according to a telephone interview	Preterm birth in pregnancies that ended in a delivery of a live singleton weighing at least 500 g between January and October 1989, determined from birth certificates and interview data	Increased risk associated with evening or night work among women who had continued working after 23 weeks of pregnancy (adjusted OR 2.0, 95% CI 1.0-3.8)
Lyon, Haguenau, France (20)	Shift and night work, based on a retrospective interview	Preterm birth, determined from data from 2 hospitals between 1977 and 1978	Increased rate in a comparison with all other type of work (RR 1.6, 95% CI 1.0-2.5)
France (21)	Night work at least partly during the first 2 trimesters, according to a retrospective interview	Preterm birth, determined from hospital records of a national sample of births in 1981	Similar rates (3.9% versus 4.8%) in a comparison with employment including no night work
Montreal, Canada (22)	Employment doing changing shift work in similar conditions for $\geq 30$ hours a week from conception until at least the 28th week of gestation, according to a retrospective interview	Preterm birth in pregnancies between 1982 and 1984 determined from medical records, and previous pregnancies, determined mainly from maternal interview data	Elevated O/E in the sales (O/E 1.6, NS) and services (O/E 1.9, $P < 0.01$ ) sectors
Anhui, China (23)	Employment in 1 of 3 textile mills in 1992 and in rotating shift work, according to a questionnaire administered by trained nurses	Preterm birth in live births, according to the questionnaire	Elevated rate in a comparison with nonrotating day work (adjusted OR 2.0, 95% CI 1.1-3.4)

in a homogeneous sample of never-smoking textile workers (23).

In some of the presented studies on preterm birth, low birthweight (ie, birthweight of  $< 2500$  g) was studied as well. Shift work was associated with low birthweight in 2 studies (22, 23), but the results of 1 study did not support this association (21).

To overcome problems due to the large overlap between preterm birth and low birthweight, in some studies on birthweight, gestational age was allowed for when birthweight was analyzed. The later results of the Montreal study by Armstrong et al (24) suggested that changing shift work retarded fetal growth and increased the risk of preterm birth as well. The mean percentage of predicted birthweight for gestational age was 98.2 (95% CI 97.2—99.2). In a Finnish study (4), mothers who had been in different types of shift work throughout most of their pregnancy had a slightly elevated risk of giving birth to babies who were small for their gestational age as compared with mothers in normal day work (adjusted rate ratio 1.4, 95% CI 0.9—2.2). When birthweight was analyzed as a continuous variable and gestational age was allowed for in the Chinese study (23), the estimated adjusted effect of rotating shift work on birthweight was -63 (standard error 42) g. In the most recent published study on shift work and preterm birth (19), night work or shift work was not related to the risk of intrauterine growth retardation. For regular evening or night work the adjusted odds ratio of having an infant that was small for its gestational age was 0.98 (95% CI 0.63—1.53) in a comparison with regular day work; for shift work the corresponding odds ratio was also 0.98 (95% CI 0.75—1.27).

### Validity aspects

The accuracy of outcome data is crucial for reliable results, and the best way to avoid misclassifying outcome is to resort to medical records whenever possible. In all of the presented studies, self-reported data on subfertility and menstrual disorders were acquired retrospectively. The feasibility of studying subfertility using retrospective self-reports has been discussed (25) and retrospective data on time to pregnancy from questionnaires have shown acceptable validity (26). In 3 of the studies on spontaneous abortion, the ascertainment of pregnancy outcome relied on the mother's recall (9, 12, 16), but the other studies used information from medical records (table 1). One of the studies on preterm birth relied only on self-reported data (23). Birthweight was acquired mainly from medical records, except in 1 study (23), but the definition of fetal growth retardation required the length of gestation, which is usually partly based on self-reported information (the first day of the last normal menstrual period).

Moreover, it is important to consider what the exposure being examined is and also what the nonexposure serving as the reference category in the comparison is. In the studies on nonstandard workhours, the type of work schedule examined varied and the applied definition of shift work was not necessarily clear. Thus it is difficult to specify entirely what features of different work schedules were actually studied or what categories of exposure were compared. The main interest areas, however, have been work involving evening and night shifts, rotating or changing schedules, and the irregularity of work patterns.

In the Swedish study on time to pregnancy (5), the data on work schedules was originally categorized as regular daytime, permanent night work, or rotating 2- or 3-shift work. Moreover, in the final analysis the different categories of nonstandard workhours were separately compared with regular daytime work. In the European multicenter study (6), information on worktime schedule was originally categorized as daytime, evening, night, or rotating shifts. In the final analysis, changing or rotating shift work was compared with the pooled category of daytime, evening, or night work. In the 2 other publications on fecundity (7, 8), the exposure was merely defined as shift work, and the comparison was with no shift work. In 2 studies on irregular menstrual cycles (9, 10), shift work including night schedules was of interest, and the comparison was with daytime work. But, in the 3rd study (11), exposure was defined as work with a varying beginning, ending or hours per week, not including night shifts. In this study, the reference category included work on a 2-shift schedule without night shifts. In 5 of the studies on spontaneous abortion (9, 12, 15, 17, 18) (table 1), some form of night work was compared with daytime work. Moreover, in 5 studies (12, 14—17), changing or rotating schedules were examined, and the comparison was mainly with daytime work (12, 14, 15, 17). In the studies on preterm birth (table 2) and fetal growth retardation (4, 19, 23, 24) the examined features of nonstandard workhours and the comparisons made differ. For example, in the recent Chinese study (23), the shift workers rotated on an 8-day week with 2 morning shifts (0600 to 1400), 2 evening shifts (1400 to 2200), 2 night shifts (2200 to 0600), and 2 days of rest. However, some night work was included in all of the schedules.

Shift work can be done in specific work environments, for example, in manufacturing, including other potentially hazardous exposures. Accordingly, in some of the reviewed studies, the study base was restricted by selection criteria already at the design stage (5, 11—15, 23) or further restricted analyses were performed to check the results (4). Moreover, especially in the most recent studies, the analyses were adjusted for other occupational exposures (4, 5, 7, 11, 12, 14, 27, 18, 19, 23). However, without reliable data, it is impossible to control potential confounding at the analysis stage and, as always in nonexperimental studies, the results can be biased by residual confounding or confounding attributable to some unrecognized factors.

The mothers with different work schedules should be comparable, or, otherwise, the results may be confounded by maternal characteristics. The outcome of pregnancy may influence the woman's choice of workhours during her next pregnancy. Therefore, in the Swedish study performed among midwives (5, 12) and in the European multicenter study (6), additional separate analyses were done for the first pregnancies to confirm the results. In

addition to the outcome of the mother's previous pregnancies, maternal characteristics that may be relevant to reproductive health include maternal age, maternal habits (such as smoking, coffee drinking, and intake of alcohol), diseases, and intake of drugs during pregnancy. Depending on the study outcome and the extent of data collection, some or many of these variables were adjusted for in the presented studies.

## Summary

Most results in connection with women's shift work concern spontaneous abortion. Seven of the 9 published studies suggest that some forms of nonstandard workhours may be associated with an increased risk of spontaneous abortion (table 1). In 4 studies (12, 14—16), the elevated risk was related to rotating schedules. In a Canadian study that demonstrated an association between pregnancy loss (spontaneous abortion or stillbirth) and evening and night work (17), rotating shift work was not associated with this outcome. Of the workers on rotating shifts, 21% worked on a night shift and 49% worked on a schedule of <35 hours a week. In the 2 completely negative studies (27, 18), rotating shifts were included in a broader exposure category and thus were not analyzed explicitly. Night work seemed to be hazardous in 3 studies (9, 12, 17), but in 2 (15, 18) no elevated risk was observed.

Preterm birth has received attention in connection with shift work as well (table 2). Combining the evidence from the studies does not provide a fully straightforward conclusion because the studied features of the nonstandard workhours and the comparisons made differed. Shift and night work (20), rotating or changing schedules (22, 23), and evening or night work (19) were related to preterm birth. However, some night work was included in all of the schedules, and thus 4 studies gave some indication that an elevated risk of preterm birth may be associated with nonstandard workhours including night work. One study found no association between the crude rates of preterm birth among women in night work at least partly during the first 2 trimesters and among women with employment including no night work (21). In 1 study (19), the time of the mother's work cessation modified the effect, and regular evening or night work seemed to be hazardous only if the mother continued working after 23 weeks of pregnancy. In the other studies, gestational age at work cessation was not taken into account explicitly.

Preterm birth is closely related to the baby's birthweight and, consequently, the occurrence of babies small for their gestational age is a more relevant reproductive outcome than low birthweight. Three studies suggest that changing or rotating shift work may retard fetal growth

(4, 23, 24), but in 1 recent study (19) shift work or regular night work were not associated with intrauterine growth retardation.

A recent study suggested that different kinds of non-standard workhours may be associated with prolonged waiting time to pregnancy (5). The study was performed on an occupationally selected and socially homogeneous population of Swedish midwives. A European multicenter study, however, associated reduced fertility only with changing or rotating shift work (6). The reported results of the European multicenter study indicated that rotating shift work was associated with subfecundity in all the countries involved. In a recently published paper, however, the authors stated that the study used the Italian data of the European multicenter study (7). The observed crude elevated risk of subfecundity was no longer seen when several occupational and maternal potential confounders were adjusted for in the analysis. Also in an earlier Danish study, shift work had no effect on subfecundity (8). It has been suggested that shift work would impair the fecundity of women by reducing sexual activity. However, in the Swedish data on time to pregnancy (5), there were no notable differences in the average frequency of intercourse between women with different work schedules. Similarly, in the European multicenter study (6), shift work did not seem to affect the level of sexual activity.

The researchers of the European multicenter study were surprised that, in their data, shift work did not increase the frequency of irregular menstrual bleedings, which has been hypothesized to be a possible cause of subfecundity. In all, 3 studies have associated some forms of nonstandard workhours with irregular menstrual cycles (9–11). In the 1992 Japanese study (10), the researchers determined plasma concentrations in subsamples from nurses working at night and nurses resting in their quarters. The findings suggested that night work suppresses the ovarian function by affecting the circadian rhythm of melatonin and prolactin.

In conclusion, the studies published on shift work and reproductive health suggest that some forms of nonstandard workhours may be associated with elevated reproductive risks, and most of the evidence is related to spontaneous abortion, preterm birth, and lowered birthweight. Although the evidence is not ample and remains ambiguous, it is prudent to consider shift work as a potential risk to reproduction.

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