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Hyperthermia and Pregnancy

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Hyperthermia is an abnormal elevation of body temperature. The normal body temperature is 98.6o F (37o C). There is concern when body temperature reaches 102o F (38.9oC) or higher during pregnancy for an extended period of time. Hyperthermia can be caused by many factors such as fever from viral infections, hot tubs, baths and saunas. This issue of RISK||NEWSLETTER will discuss hyperthermia and its effects on pregnancy.

In considering the teratogenicity of hyperthermia, the timing of hyperthermia during development, degree of elevation and duration of elevation must be examined. Genetic factors may also be involved in hyperthermia and teratogenicity, but these have not been studied in humans.

ANIMAL STUDIES

Hyperthermia has been studied in numerous animal models, including rodents, guinea pigs, lambs and monkeys. In all species studied, the central nervous system appeared to be at greatest risk of damage from hyperthermia during pregnancy (Reprotox, 1996). A wide range of other abnormalities have been found when temperatures were raised several degrees above normal core body temperature in animals. These abnormalities include microcephaly; defects of the eye and palate; maxillary hypoplasia; limb reduction defects; renal agenesis; and, learning impairment (Skreb et al., 1963; Hofmann et al., 1966; Edwards, 1969; German et al., 1985; Sasaki et al., 1995; Shiota et al., 1989; Harding et al., 1993).

A critical teratogenic threshold temperature has been observed in numerous animal studies. In mammals, the critical teratogenic threshold elevation is 2.0o to 2.5oC above the normal core body temperature (Edwards et al., 1995). This has been seen in pigs, rats, rabbits, sheep and guinea pigs. In humans, researchers have suggested that the threshold temperature for teratogenicity is 38.9oC (102o F) (Smith, 1981; Harvey et al., 1981).

Additionally, the longer the duration of temperature elevation, the higher the risk of teratogenic effects. Studies in rats seem to indicate that as the temperature is elevated, the amount of time required to produce defects is decreased in a logarithmic fashion (Germaine et al., 1985).

HUMAN STUDIES

Neural Tube Defects

Numerous epidemiological studies suggest that there is an association between hyperthermia and an increased incidence of neural tube defects. The incidence of neural tube defects in the general population is 1/1000-2/1000.

Retrospective studies of women who had children with neural tube defects found that a notable

proportion of these women had a fever early in pregnancy. Christo et al. (1987) studied the pregnancy history of the mothers of 30 children born with central nervous system abnormalities and found that 4 (13%) of the mothers had significant fevers during the first trimester. Layde et al. (1980) interviewed mothers of children with neural tube defects as well as mothers of children with Down syndrome as a control for memory bias. He found that there was a higher incidence of fever during the first trimester in the neural tube defect group when compared to the control group. In a larger study, Hunter (1984) interviewed 264 women who gave birth to children with neural tube defects between 1961 and 1981 and found that 32 (12%) reported fevers during pregnancy. Thirteen of these women reported that the fever occurred within the first four weeks of pregnancy. Nine out of the 13 women had children with anencephaly.

Milunsky et al. (1992) conducted a large-scale prospective study that used a cohort of 23,491 women who were receiving prenatal care or having amniocentesis. He found that fever during the first trimester of pregnancy was associated with an increased risk for neural tube defects. The relative risk, adjusted for maternal age, folic acid supplements, family history of neural tube defects and exposure to other heat sources, was found to be 1.8 (95% CI, 0.8 to 4.1).

The central nervous system begins to form during the third week after conception with neural tube closure occurring by 18-28 days. The central nervous system also continues to develop throughout pregnancy, making it more susceptible than other systems. After the eighth week post-conception or the end of the organogenesis period, organ systems are less susceptible to damage.

Spontaneous Abortion

Hyperthermia during pregnancy has also been associated with spontaneous abortion. Kline et al. (1985) conducted a case-control study to examine the possible association of maternal fever during pregnancy and spontaneous abortion. Women with fevers of 100oF (37.78oC) were divided into three groups: women having euploid abortions, women having aneuploid abortions and women delivering at 28 weeks gestation or later (control group). The researchers hypothesized that there was an association between maternal fever and spontaneous euploid abortions. Fevers were more prevalent in euploid abortions than among the control group (18% vs. 7.1%, odds ratio =2.96). Fevers were not significantly more frequent in aneuploid abortions (3.9% vs. 7.1%, odds ratio=0.52). The timing of fever and spontaneous abortion was studied as well. The odds ratio for fever occurring during three different intervals before spontaneous abortion was evaluated. For euploid abortion within a month of the fever, the odds ratio was 6.04. For fever one month before abortion, the odds ratio was 3.28, while for fever two months before spontaneous abortion, the odds ratio was calculated to be 1.41. Both public and private patients were studied. There was no statistical significance between the two groups. In a prospective study by McDonald (1958, 1961), that looked at 3144 pregnancies, it was reported that there was an increased incidence of spontaneous abortion and children with major congenital defects as compared to the general population.

Other Abnormalities

In addition to the effects of maternal hyperthermia on the central nervous system and possible association with spontaneous abortion, hyperthermia in relation to other abnormalities has been examined. Tikkanen et al. (1991) conducted a retrospective case-control study of 573 women in Finland who gave birth to children with cardiovascular defects. Maternal fever was found to be more prevalent in mothers of children with cardiovascular abnormalities (10%) than in the case controls (6%) ($p<0.01$). The most common cardiovascular abnormalities were atrial septal defect and hypoplastic left heart. Fraser and Skelton (1978) randomly reviewed records of children with congenital defects over a 25 year period from Montreal Children's Hospital to ascertain if any particular defect was associated with maternal fever. They found that fever during the first five months of pregnancy was associated

with a significant increase of microphthalmia, hypospadias and congenital heart disorders. A series of studies were conducted of women who had hyperthermia during pregnancy and an association between hyperthermia and myelomeningocele, occipital encephalocele, severe mental deficiency, seizures, hypotonia, microphthalmia, midface hypoplasia and limb defects was found. Structural and functional disturbances in the central nervous system were the most common findings (Chance et al., 1978; Smith et al., 1978; Pleet et al., 1980; Pleet et al., 1981). These findings in humans were similar to that found in studies by Edwards (1967; 1969; 1969) in guinea pigs and rats. Little et al. (1991) conducted a study of 54 women who experienced fever of 101oF (38.3oC) or higher for over 24 hours during the first trimester and compared them to a control group of women matched for last menstrual period, parity and age. A statistically significant increase in frequency of congenital abdominal wall defects (5 of 54 children) were found in the offspring of women who experienced fever.

Negative Studies

Some studies have not found an association between hyperthermia and adverse pregnancy outcome. The Collaborative Perinatal Project prospectively studied 55,000 pregnancies; 165 women reported having fevers of 102oF (38.9oC) for 1-3 days during the first trimester of pregnancy (Claren et al., 1979). When this group was matched against a control group, no difference in the incidence of congenital abnormalities, spontaneous abortion, stillbirths, preterm births or neurological defects were found. Kleinebrecht et al. (1979) found no significant increase in eye or neural tube defects in children of women who experienced fever during the first trimester.

SAUNAS AND HOT TUBS

Some studies have suggested that sauna use during pregnancy could be the cause of congenital malformations. In Finland, where a majority of the women visit saunas regularly during pregnancy, studies have reported no increase in central nervous system defects. However, the incidence of neural tube defects was among the lowest reported (Edwards et al., 1995). This low rate could possibly be due to a low genetic susceptibility in Finnish women. Saxen et al. (1982) studied 100 consecutive cases of central nervous system defects and 202 cases of orofacial clefts from the Finnish Registry of Malformations. No difference in sauna habits were found between these mothers and the control group. In a comparison study of sauna use in Finland and Australia, Finnish women appeared to have a number of short exposures with intervening cooling periods, while Australian women had one long exposure to the point of discomfort. Because of short exposure time, it had been suggested that it was unlikely that the core body temperature of Finnish women increased above threshold levels to cause any teratogenic effects (Uhari et al., 1979).

Milunsky et al. (1992) studied 23,491 women prospectively and found that there was a relative risk of 1.8 (95% CI, 0.4 to 7.9) for sauna use during pregnancy. This relative risk was adjusted for other variables, including folic acid supplements, family history of neural tube defects, exposure to other heat sources and maternal age.

Bathing in hot tubs can elevate core body temperatures much more quickly than saunas. Sauna use permits greater heat loss through evaporation of perspiration. It has been recommended that maternal body temperature should not exceed 38.9oC (102oF) (Harvey, 1981). In the prospective study by Milunsky et al. (1992) the relative risk of maternal use of hot tubs during pregnancy was found to be 2.8 (95% CI, 1.2 to 6.5). For hot tub use it has been recommended that pregnant women limit their exposure to 15 minutes in 39oC (102.2o F) water or to 10 minutes in 40-41oC (104-106oF) (Harvey et al., 1981; Ridge et al., 1990). The overall relative risk for exposure to either hot tubs, saunas or fever was calculated to be 1.9 (95% CI, 0.9 to 3.7). The relative risk increases three-fold, to 6.5 (95% CI, 2.2 to 17.2) after two types of heat exposures occur (Milunsky et al., 1992).

SUMMARY

Numerous studies suggest that hyperthermia during early pregnancy is associated with neural tube defects. As the neural tube closure occurs by the 28th day after conception, hyperthermia during early pregnancy could interfere with proper closure. Hyperthermia may also be associated with an increased risk for spontaneous abortion and congenital defects including microphthalmia, distal limb defects, hypotonia and cardiovascular abnormalities.

Saunas and hot tubs can also place the pregnant woman at risk for hyperthermia. It is recommended that core body temperatures be kept below 38.9°C (102°F). Hot tub bathing should be limited to 15 minutes in 39°C (102.2°F) water or to 10 minutes in 40-41°C (104-106°F).

Prenatal diagnosis can detect a vast majority of open neural tube defects. Maternal serum alpha-fetoprotein (MSAFP) screening between 15-18 weeks can identify 80% of open neural tube defects. Ultrasound during the second trimester can detect 80-90% of open neural tube defects, as well as other major structural abnormalities. Women with histories of hyperthermia should be prenatally evaluated by MSAFP and ultrasound for any structural abnormalities.