Exercise at High Temperature Causes Maternal Hyperthermia and Fetal Anomalies in Rats

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ABSTRACT

Hyperthermia is thought to be a teratogen in many animal species and also in humans. It has been reported that hyperthermia caused by sauna, hot tub, or fever during the early stages of pregnancy is related to an increased risk for neural tube defects. During exercise, especially in hot conditions, body temperature can also rise to fairly high levels. Thus, we can surmise that hyperthermia induced by exercise can also cause fetal malformation.

To investigate this hypothesis, pregnant rats at 9 days of gestation were divided into four groups. In the first group, the animals were made to swim for 30 minutes in water at a temperature of 40.5°C. In the second group, they were restrained and immersed in water for the same time at the same temperature. In the third group, the rats were forced to swim in water at 36.0°C. The fourth group were controls. The core temperature of the rats was measured during these procedures. On the 18th gestational day, fetuses were extracted by cesarean section. The elevation of maternal core temperature was significantly greater in the first group than in the other groups. In the first group, 69% of fetuses had various external anomalies. No anomalies were found in the other groups.

Our results show that exercise in hot conditions caused the elevation of core temperature and resulted in fetal anomalies in rats. © 1995 Wiley-Liss, Inc.

MATERIALS AND METHODS

The study protocols were approved by the Committee of the Laboratory Animal Research Center of the University of Tsukuba. Female Sprague-Dawley rats (8–10 weeks old) were mated to males of proven fertility. The following morning, when a vaginal plug was observed, was designated as day 0 of pregnancy. The animals were kept in one room at a constant temperature (23±1°C) and under a controlled 14-hour day/10-hour night cycle. They were allowed free access to food and water.

At 9 days of gestation, they were divided into four groups. In the first group, the rats were forced to swim in a water bath at a temperature of 40.5°C for 30 minutes. In the second group, the animals were restrained in a wire net and immersed to the neck in a water bath of the same temperature for 30 minutes. In the third group, the rats were forced to swim in a water bath at a temperature of 36.0°C. In the fourth group, the rats were not forced to undergo any adverse conditions. The bath tub was a large polyvinyl bucket with a diameter of 50 cm and a depth of water of 45 cm. The thermister probe (TERUMO, PD-K061) was set at a depth of 10 cm below the surface of the water. Water was stirred by air which was set at a constant flow rate. In the first to third group, the same thermister probe was inserted into the rectum of the animal to a depth of 4.5 cm and fixed to the tail. Both water and animals’ core temperatures were constantly monitored by thermometer (TERUMO, CTM-303). Readings were taken 3 minutes before immersion, at 30 second intervals during immersion, and 5 minutes following.

On the 18th gestational day, the mother was killed and fetuses were extracted by cesarean section. Fetuses were all individually weighed and their gross external malformations were examined. For statistical analysis, ANOVA was undertaken when fetal weight, maternal

In recent years, there has been a dramatic increase in the number of women engaging in various kinds of sports, and even pregnant women are no exception. In pregnant women, however, a problem that should be considered is the effect of exercise not only on the mother but also on her fetus. The potential fetal risks in exercising women are abortion, premature labor, fetal distress and intrauterine growth retardation (Mittemark et al., '91). Another disadvantage is a possibility of inducing fetal malformation caused by maternal hyperthermia in early pregnancy. In this report, we try to answer the question whether fetal anomaly can be caused by hyperthermia during exercise.

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maximal temperature and the time in which maternal core temperature was above a certain temperature level were compared. Differences in the frequencies of fetal anomaly, early resorption or intrauterine fetal death among four groups were tested by Fisher's exact test. The level of statistical significance used in the study was $P<0.05$.

RESULTS

We found an elevation of core temperature in all the mother rats of both swimming and immersion only groups using the $40.5^\circ C$ bath. In the first group, core temperature rose rapidly and reached the plateau (around $42.0^\circ C$) in 10 to 15 minutes. It remained stable for 15 to 20 minutes, then after the rats were taken out of the water, the temperature went down abruptly. In the second group, core temperature rose gradually, and reached a plateau between 15 to 20 minutes. In the third group, no change of core temperature was observed (Fig. 1).

In the first group, the durations of cumulative time in which the core temperature was above 40.0, 40.5, 41.0, 41.5, 42.0 and 42.5°C were $31.3 \pm 1.0$, $28.9 \pm 1.1$, $27.6 \pm 1.3$, $24.5 \pm 1.8$, $18.9 \pm 4.6$ and $0.3 \pm 0.8$ (mean ± S.D.) minutes, respectively. In the second group, they were $27.8 \pm 1.1$, $24.6 \pm 1.4$, $20.2 \pm 1.9$, $7.6 \pm 8.4$, $0.4 \pm 1.0$, and 0 minutes, respectively. At each division, except for above $42.5^\circ C$, significant elongation of times were noted in the first group compared with the second group ($P<0.001$). In the third group, the core temperature never exceeded $42.0^\circ C$ (Fig. 2).

The maximal core temperature was $42.3 \pm 0.2^\circ C$ in the first group, $41.6 \pm 0.3^\circ C$ in the second group, and $38.9 \pm 0.2^\circ C$ in the third group, respectively. The maximal core temperature in the first group was significantly higher than in the other groups ($P<0.001$).

In the first group, 69% of fetuses had various kinds of anomalies with incidences significantly higher than the other groups ($P<0.001$). Also in the first group, 5% of fetuses were aborted and 2% suffered intrauterine death. These incidences were not significant compared with the other groups.

In the second group, no malformation or early resorption was seen. There was only one intrauterine death. In the third group and nontreatment group (fourth group), neither malformation, abortion nor intrauterine death was observed.

In the first group, the weights of the live fetuses were significantly smaller ($P<0.05$ compared with the second and fourth group; $P<0.01$ compared with the third
group) than those in the other groups. Among other groups fetal weight remained constant (Table 1).

In the first group, the most common types of anomalies were microphthalmia and anophthalmia, which 69% of fetuses suffered. Encephalocele (45%), mandibular hypoplasia (22%), maxillary hypoplasia (20%) and gastroschisis (14%) were also seen. The combination of several kinds of defects were often seen (Table 2).

**DISCUSSION**

In this study, the cause of fetal defects is thought to be hyperthermia induced by exercise in hot conditions. As there were no malformations observed in the second and third groups, immersion itself or swimming itself cannot be seen as the basic causes of malformation.

Our results indicate that there is a "threshold dose" which is a product of the level of temperature elevation and the duration of elevation. An earlier study by Germain et al. ('85) also reported the existence of the threshold dose. They made clear that the core temperature rose to the threshold dose and not the means by which it is achieved.

Maternal hyperthermia has been shown to be a teratogenic agent in many animal species (Edwards, '81) and also in humans (Miller et al., '78; Smith et al., '78; Shiota, '82; Milusky et al., '92). Milusky et al. ('92) reported that exposure to heat in the form of hot tub, sauna, or fever in the first trimester of pregnancy was associated with an increased risk of neural tube defects. Sohar et al. ('76) revealed that during 20 minutes of Finnish sauna bathing, core temperature rose to 38.6 ± 0.6°C. The studies of Smith et al. ('78) showed that maternal febrile disease causing the body temperature to rise above 38.9°C in the early stage of pregnancy was associated with fetal anomaly. Thus, the critical body temperature for the human fetus is thought to be approximately 39°C.

During moderate or recreational physical activity, the body temperature rarely exceeds 39°C (McMurray et al., '93; Brown et al., '93; Madsen et al., '93; Clapp III, '91). But during more rigorous physical activity, the body temperature has been seen to exceed 39°C (Clapp III et al., '87; Ryan et al., '91; Rozycki, '84), especially during competition. It was reported to reach 39.7°C after only a 5 km running race (Robinson, '63). In marathon running, body temperature has been reported to reach 39.0±1.0°C (Pugh et al., '67) or 39.8±0.7°C (Maron et al., '75) or even 41.7°C (Maron et al., '77). Furthermore, under conditions of high environmental temperature and humidity, the increase in body temperature can exceed the critical level at much lower exercise intensities (Robinson, '63; Paolone et al., '78).

The ninth day of gestation in rats corresponds to the fourth week of gestation in humans. For women who wish to participate in moderate or recreational physical activity during the early stages of pregnancy, elevation of body temperature to the critical level is prob-

### TABLE 1. Fetal outcome of each group

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of dams</th>
<th>Total number of implants</th>
<th>Normal fetuses no. (%)</th>
<th>Fetal anomalies</th>
<th>Weight of live fetuses (mean ± S.D., g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First group (swimming)</td>
<td>6</td>
<td>85</td>
<td>20 (24)</td>
<td>59 (69)***</td>
<td>1.10 ± 0.27***</td>
</tr>
<tr>
<td>(bath temp.: 40.5°C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second group (restrained)</td>
<td>6</td>
<td>88</td>
<td>87 (99)</td>
<td>0 (0)</td>
<td>1.37 ± 0.12</td>
</tr>
<tr>
<td>(bath temp.: 40.5°C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Third group (swimming)</td>
<td>6</td>
<td>94</td>
<td>94 (100)</td>
<td>0 (0)</td>
<td>1.40 ± 0.09</td>
</tr>
<tr>
<td>(bath temp.: 36.0°C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fourth group (no treatment)</td>
<td>6</td>
<td>81</td>
<td>81 (100)</td>
<td>0 (0)</td>
<td>1.39 ± 0.10</td>
</tr>
</tbody>
</table>

***Significantly increased compared with the other groups (P<0.001).
**Significantly decreased compared with the other groups (*P<0.05, compared with the second and fourth group, **P<0.01, compared with the third group).

### TABLE 2. The type of anomalies seen in the first group

<table>
<thead>
<tr>
<th>Type of anomaly</th>
<th>No.</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microphthalmia/anophthalmia</td>
<td>59</td>
<td>69</td>
</tr>
<tr>
<td>Encephalocele</td>
<td>38</td>
<td>45</td>
</tr>
<tr>
<td>Mandibular hypoplasia</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td>Maxillary hypoplasia</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>Gastroschisis</td>
<td>12</td>
<td>14</td>
</tr>
</tbody>
</table>
ably not a major concern. However, our results indicate that if strenuous physical activity is undertaken during this period, birth defects may occur. In the early stages of pregnancy, a woman may not know whether she is pregnant. Therefore, it is advised that women who want to participate in strenuous physical activity should either use contraceptives, or if already pregnant, reduce the intensity of their training.

Since, to our knowledge, there has been no report dealing with the birth results of women who continued to participate in rigorous physical activity during the early stages of pregnancy, further study is necessary.

LITERATURE CITED


