Effects of exercise in diabetic rats before and during gestation on maternal and neonatal outcomes

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VanHeest, Jaci L., and Carol D. Rodgers. Effects of exercise in diabetic rats before and during gestation on maternal and neonatal outcomes. Am. J. Physiol. 273 (Endocrinol. Metab. 36): E727–E733, 1997.—This study was designed to evaluate the effects of chronic endurance training on glucose and lipid homeostasis in diabetic mothers and their offspring. Female Sprague-Dawley rats were rendered diabetic (>20 mmol/l glucose) by streptozotocin and subdivided into three treatments (n = 10/group): exercise (20 m/min; 0% grade; 1 h/day; 5 days/wk) before and during gestation (EE), exercise before gestation with cessation on conception (ES), and sedentary before and during gestation (SS). Response of dams to a preconception and third trimester glucose tolerance test, litter number (EE = ES = SS = 3), and average litter size (EE = 9.7 ± 1.5; ES = 9.0 ± 1.5; SS = 8.3 ± 0.3) did not differ among groups. Number of offspring remaining viable was significantly different among groups (EE = 17; ES = 6; SS = 14). Response to a glucose challenge and fasting glucose and insulin were different between the EE and SS pups. Exercise before and during gestation did not reduce the viability of offspring. Cessation of exercise during early pregnancy negatively affected offspring viability.

insulin-dependent diabetes mellitus; glucose metabolism; lipid metabolism; teratology

IT IS WELL RECOGNIZED that the combined stress of insulin-dependent diabetes mellitus (IDDM) and pregnancy creates a metabolic environment that is often life threatening to both the mother and the fetus (9, 18). This is primarily due to increased difficulty with diabetes control in the mother, which occurs because of the natural diabetogenic state of pregnancy. The maternal environment is altered, and a situation is created in which the fetus is exposed to abnormal metabolic substrate levels. The compromised metabolic state of the fetus subsequently precipitates a variety of complications associated with “fuel-mediated teratogenesis” (e.g., hyperinsulinemia, macrosomia, and hyperglycemia) (9, 18). The period during gestation when the fetus is affected determines both the degree and the specific location of the teratogenic abnormalities that occur.

Gauguier et al. (10) simulated a moderate hyperglycemic state during the latter part of pregnancy and found that the offspring of hyperglycemic dams showed changes at birth and into adulthood similar to those typically exhibited by newborns from diabetic mothers. It is apparent from these data that modifications in placental transfer have a significant impact on the overall well-being of the fetus. It stands to reason, therefore, that any intervention either before or during pregnancy that would improve the metabolic status of the mother and/or improve the nature of placental transfer would positively benefit both the mother and the fetus. Exercise might be one such intervention.

Urie-Hare and colleagues (25) demonstrated a positive effect of exercise training 3 wk before and during gestation on fetal weight and morphological development in offspring of diabetic rats. Maternal circulating free fatty acid and triglyceride levels were also improved by exercise training before and/or during gestation in diabetic rats (12, 13). However, these studies are limited by the shortness of the period of exercise training before conception and the interference of the simultaneous induction of the diabetic state and exercise training. Exercise training is known to result in improved insulin sensitivity, enhanced muscle enzyme activity, and an improved lipid profile in both diabetic and nondiabetic individuals (20). One hypothesis of this study is that exercise training will enhance the ability of the mother to handle the metabolic alterations associated with a diabetic pregnancy and thereby improve both maternal and offspring outcome.

Cessation of exercise near the time of conception may seem rather inconsequential; however, it has been shown to negatively impact offspring outcome in nondiabetic animals. Mottola and Christopher (19) demonstrated that offspring from nondiabetic dams that stopped exercise on conception were smaller and had lower liver glycogen levels than pups from mothers who continued to exercise during gestation. The metabolic environment appears to have placed the fetus in a significantly compromised state.

Therefore, the purposes of the present study were to 1) examine the role of endurance training before and during gestation on maternal metabolic response to pregnancy, 2) evaluate the effects of terminating exercise in conjunction with the onset of pregnancy, 3) determine whether exercise training before and during pregnancy affects offspring outcomes, and 4) illustrate the relationship between offspring growth patterns and glucose handling.

METHODS

Maternal

Animal care and monitoring. Female Harlan Sprague-Dawley (Madison, WI) rats (150–175 g) were housed in separate nalgene cages in a pathogen-free University Laboratory Animal Research facility. Food (Purina Rat Chow 5008) and water were supplied ad libitum, and the animals were kept on a 12:12-h light-dark cycle (0100:1300). Room temperature (70–74°F) and humidity (50–54%) were controlled throughout the study to ensure the health of the animals. Experimental procedures were approved by the University Animal Experimentation Ethics Committee.
On arrival at the facility, the animals were allowed 6 days to become familiarized with their new environment in the animal facility. Each animal was weighed daily during this time to familiarize it with its caretakers. Subsequently, all animals were weighed weekly during the preconception portion of the study and daily during gestation. Food intake was also measured on a weekly basis for each animal.

Diabetes induction. A 2-h fasting arterial blood sample (1 ml) was drawn from the tail artery (3) of each animal 6 days after its arrival. Samples were immediately centrifuged for 25 min at 1,500 g, and the serum was stored at −20°C for later analysis of blood glucose concentration representative of the prediabetic status of the animals. Two days after their respective draw, animals were injected with a 50 mg/kg body mass dose of streptozotocin (STZ; S-0130; Sigma Chemical, St. Louis, MO) into the tail vein. The STZ was dissolved in 40 mM citrate buffer (pH 4.5), and care was taken to ensure that the STZ injection occurred within 5 min of dissolution in citrate to allow for the STZ to be in its active state (5). All animals were anesthetized by methoxyflurane inhalation before arterial blood sampling and STZ injection.

Diabetes evaluation. After STZ injection, animals were maintained for 14 days without further intervention to enable the diabetogenic effects of STZ to be expressed (13). An arterial blood sample (1 ml) was then drawn and analyzed for serum glucose and insulin levels (day 0) to determine each animal’s level of diabetes. Forty-eight hours after day 0 measurements, an intraperitoneal glucose tolerance test (IPGTT) [glucose tolerance test 1 (GT1)] was administered to those animals that had attained a minimal blood glucose level of 20 mmol/L. Each animal (n = 30) received a 2 g/kg body mass dose of 30% glucose intraperitoneally in a fasted state (2 h). Blood samples (0.1 ml) were collected from the tail vein (3) of restrained animals. Samples were drawn 10 min before injection of glucose and 10, 30, 60, and 120 min after injection. Samples were centrifuged (25 min at 1,500 g), stored (−20°C), and later analyzed for serum glucose concentration at each time point. The area under the GTT curve was calculated for GTT1 and all subsequent IPGTTS. Animals (n = 30) were then matched in groups of three, based on body weight and blood glucose response to GTT1 (initial and peak values). One animal from each trio was then randomly assigned to one of the following three groups: the sedentary before and during gestation (SS; n = 10), the exercise before but sedentary during gestation (ES; n = 10), or the exercise before and during gestation (EE; n = 10) treatment group.

Exercise program. EE and ES animals initiated their exercise program by running on a motor-driven treadmill for a 14-day adaptation period. The animals began running at 10 m/min, 0% grade, 15 min/day, 5 days/wk and increased to a level of 20 m/min, 0% grade, 60 min/day, 5 days/wk by day 14. We encouraged the animals to run by touching the rear of the animal. Animals that did not comply with the adaptation protocol were removed from the study. The animals continued to train at this final intensity for 8 wk before mating. The nonexercising group remained sedentary during this time period but was exposed to the same environmental conditions as the runners during the training sessions. All exercise sessions were conducted during each animal’s dark cycle. The animals in the sedentary groups had no access to food and water during the time period corresponding to the exercise bouts. Arterial blood was obtained from all animals at weeks 2, 4, and 6 of the training program. Serum was frozen for later analysis of glucose, insulin, and cholesterol. On completion of this preconception training program (after week 8), a second IPGTT (GT2) was performed on animals in all groups. Animals in the EE group continued to exercise during gestation, whereas ES and SS animals were sedentary.

Impregnation and gestation monitoring procedures. Twenty-four to forty-eight hours after GTT2, each animal was injected with 50 µg of luteinizing hormone-releasing hormone (LHRH; Sigma Chemical no. L-4563). The LHRH was carried in a 0.1% bovine serum albumin solution with the total injected volume of the active hormone being 0.2 ml per animal (19). The LHRH primes for estrus to occur during the 12-h dark cycle 110 h postinjection period. Animals were allowed to mate with a breeder male (Harlan Sprague Dawley) during the 12-h dark cycle (19). After the mating period, each female was evaluated for a vaginal sperm plug and a positive vaginal smear. Positive evaluations were described as day 0 of gestation (GD0). No animal was allowed to be injected or mated more than one time during the course of the study; therefore, any animal that did not become pregnant was removed from the study.

A final IPGTT (GT3) was administered on day 19 of gestation (GD19). This time point was chosen to ensure that the animals were in a third trimester condition as well as to minimize the risk of negatively influencing birthing procedures. The mothers were then allowed to birth their pups naturally. Within 8 h postpartum, the neonates were weighed and evaluated for gross morphological abnormalities. After evaluation, pups from diabetic dams were given to euglycemic foster mothers to minimize any influence of milk contribution on growth and insulin sensitivity of the offspring. All animals were allowed to nurse freely and were weaned at 21 days of age.

Maternal and Offspring Outcomes

Maternal evaluation. After the fostering procedure, diabetic dams from all groups (EE, ES, SS) were anesthetized via methoxyflurane inhalation before surgical removal of tissues (heart, liver, and skeletal muscle). On completion of the surgical tissue harvesting, the animals were exsanguinated with the use of a pneumothorax technique.

Offspring. Offspring were gendered, weighed, and assessed for gross morphological abnormalities at the time of birth. In addition, the pups were weighed weekly for the subsequent 4 wk. Several pups from the foster mothers were kept with the offspring from the diabetic dams. The mixed litters were allowed to mature without intervention. This method allowed for the natural offspring of the foster mother to be used as a control group for the pups of the diabetic mother. These animals are denoted as control (C).

At 28 days of age, offspring were given a fasting (12 h) IPGTT (3 g/kg body mass; 50% glucose). Blood samples (0.1 ml) were collected from the tail vein before injection of glucose load and 10, 30, 60, and 120 min after injection (3). Samples were centrifuged (1,500 g; 20 min) and stored at −20°C until later analysis of plasma glucose levels at each time point.

Twenty-four hours after administration of the GTT, each animal was anesthetized with methoxyflurane, and surgical removal of the soleus, plantaris, and gastrocnemius muscles, heart, and liver was performed. Nonfasting blood was obtained from the heart before exsanguination by pneumothorax and later analyzed for plasma glucose, insulin, and cholesterol concentrations.

Blood Evaluation

Glucose levels were determined using the glucose oxidase method on a Kodak Ektachem DT60 analyzer. Insulin levels were analyzed using radioimmunoassay (rat insulin kit; Linco, St. Louis, MO). Total cholesterol levels were assayed using a cholesterol kit from Sigma Chemical (no. 352).
Statistical Analysis

Analysis of variance (ANOVA) with repeated measures was used to determine the effects of treatment and time on response (area under the curve and glucose concentration) to the IPGTT. Tissue and body weights at the time of death were analyzed by a factorial ANOVA. Finally, litter size, resorption number, and viable neonate number were compared with a factorial ANOVA. Post hoc Scheffé’s analysis was utilized to assess for significant pairwise differences when appropriate. The level of significance was chosen at $P < 0.05$ in all instances. All values reported are expressed as means ± SE.

RESULTS

Maternal

Body mass and food intake. Figure 1A illustrates mean body weight across the preconception period. Body mass increased steadily in all groups until week 8, at which point a plateau was achieved. There was no significant difference in body mass among the groups at any of the time points examined. Weekly food consumption in all groups increased through week 4 and then was maintained at this new level through the remainder of the preconception phase.

Body mass during gestation is illustrated in Fig. 1B. All groups had similar values at GD0, with group averages (for all 3 groups) ranging from 216 ± 5.86 to 258 ± 8.99 g. As expected, there was a steady increase in body weight over time in those animals that became pregnant. There was no significant difference in body mass gain during gestation among EE, ES, and SS groups. ES animals were, however, consistently heavier throughout gestation than either of the other two pregnant groups. Food intake during the gestational period was not significantly different among groups.

Resting arterial blood levels. Blood glucose, insulin, and cholesterol values, as determined throughout the study, are presented in Table 1. Administration of a 50 mg/kg body mass dose of STZ caused a significant increase in arterial blood glucose concentration within 2 wk of injection (glucose concentration > 20 mmol/l). Subsequent 2-h fasting arterial plasma glucose levels did not differ significantly among groups at any of the time points examined during the 8 wk before mating or when animals were killed after gestation.

Table 1. Arterial blood values from diabetic animals

<table>
<thead>
<tr>
<th></th>
<th>Week</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>Death</td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EE</td>
<td>23.4 ± 1.9</td>
<td>31.3 ± 0.7</td>
<td>32.9 ± 3.9</td>
<td>31.5 ± 3.3</td>
<td>34.4 ± 4.6</td>
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<tr>
<td>ES</td>
<td>20.9 ± 0.9</td>
<td>24.7 ± 3.5</td>
<td>30.9 ± 1.9</td>
<td>32.9 ± 3.9</td>
<td>35.8 ± 3.9</td>
</tr>
<tr>
<td>SS</td>
<td>20.2 ± 0.9</td>
<td>29.4 ± 2.1</td>
<td>30.3 ± 1.7</td>
<td>34.5 ± 2.6</td>
<td>34.9 ± 2.9</td>
</tr>
<tr>
<td>Insulin, ng/ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EE</td>
<td>0.1 ± 0.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ES</td>
<td>0.7 ± 0.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SS</td>
<td>0.2 ± 0.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol, mg/dl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EE</td>
<td>122.4 ± 6.9*</td>
<td>126.3 ± 10.7*</td>
<td>133.8 ± 21.2*</td>
<td>197.5 ± 14.5</td>
<td></td>
</tr>
<tr>
<td>ES</td>
<td>129.6 ± 10.5</td>
<td>139.7 ± 5.9</td>
<td>147.0 ± 14.2</td>
<td>126.8 ± 12.3</td>
<td></td>
</tr>
<tr>
<td>SS</td>
<td>125.3 ± 15.5</td>
<td>129.9 ± 11.2</td>
<td>131.9 ± 16.8</td>
<td>142.4 ± 17.1</td>
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</tr>
</tbody>
</table>

Data represent means ± SE for 10 animals/group at weeks 0, 2, 4, and 6 of training. Data at time of death are for pregnant animals (n = 3 animals/group). EE, exercise before and during gestation; ES, exercise before gestation with cessation on conception; SS, sedentary before and during gestation. *$P < 0.05$ vs. timepoint at death.
Insulin values were not significantly different among the groups at time of death. Cholesterol values were not different among any of the groups. However, EE animals had significantly lower cholesterol values at all times evaluated compared with levels at time of death.

Response to an IPGTT. During the preconception period, two IPGTTs were administered, the first (GTT1) 2 wk after administration of STZ and the second (GTT2) at the end of the 8-wk training phase (Fig. 2A). Animals in all groups exhibited an elevated response to the intraperitoneal glucose load typical of their diabetic state during both GTT1 and GTT2. There was no significant difference among groups in serum glucose levels achieved at any of the time points during GTT2 (Fig. 2A). Calculation of the area under the glucose curve for GTT2 for those animals that became pregnant resulted in the greatest area attained by the EE group and the smallest by the ES group.

Results from the GD19 GTT are provided in Fig. 2B. As expected, animals in the pregnant groups had a blunted response to the intraperitoneal glucose load in comparison with their posttraining, preconception GTT. Concentrations of glucose at time points measured were not significantly different among groups at GD19. Area under the curve at GD19 was not different among groups.

Table 2. Offspring outcomes at birth

<table>
<thead>
<tr>
<th>Parameter</th>
<th>EE</th>
<th>ES</th>
<th>SS</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of litters</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Litter size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total pups</td>
<td>29</td>
<td>27</td>
<td>25</td>
</tr>
<tr>
<td>Average</td>
<td>9.67 ± 1.45</td>
<td>9.00 ± 1.53</td>
<td>8.33 ± 0.33</td>
</tr>
<tr>
<td>Viable pups</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>17*</td>
<td>0</td>
<td>14*</td>
</tr>
<tr>
<td>Average/litter</td>
<td>5.67 ± 3.18</td>
<td>0</td>
<td>4.67 ± 2.40</td>
</tr>
<tr>
<td>Total resorption sites</td>
<td>6</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Total male offspring</td>
<td>14</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Total female offspring</td>
<td>15</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Viable pup body mass, g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male offspring</td>
<td>5.43 ± 0.29</td>
<td>6.15 ± 0.75</td>
<td></td>
</tr>
<tr>
<td>Female offspring</td>
<td>4.77 ± 0.07</td>
<td>5.43 ± 0.09</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as means ± SE. Thirty percent of animals in each treatment became pregnant. *P < 0.05 vs. ES group.

Offspring

Birth outcomes. Offspring outcome data for the three pregnant groups are presented in Table 2. Number of litters, litter size, and resorption site number did not differ significantly among the three groups. There were no viable offspring from the ES dams, whereas the number of offspring from EE and SS mothers was similar (EE = 17; SS = 14).

Body mass changes. The effect of maternal activity status on offspring body weight is illustrated in Fig. 3. At days 0, 7, 14, and 21, C offspring were significantly heavier than offspring of EE and SS dams. Maternal activity condition had no significant effect on offspring body weight at day 28.

Response to an IPGTT. An IPGTT was administered to all offspring at 28 days of age. Plasma glucose response to the glucose load is illustrated in Fig. 4. In general, offspring from EE mothers presented a blunted response, whereas pups from SS dams showed augmented glucose levels. Twelve-hour fasting plasma glucose concentration was significantly lower in offspring of EE dams than in offspring of C and SS mothers. The difference between SS and EE offspring...
between-group difference existed between the SS and both the EE and C pups for heart and red gastrocnemius muscle weights assessed at 28 days.

**DISCUSSION**

The present study was designed to evaluate the effects of chronic endurance training on glucose and lipid homeostasis in both diabetic mothers and their offspring. A unique feature of this study was that it enabled a thorough examination of the interaction between exercise training and pregnancy and the effect of this interaction on pregnancy outcome. To date, no other study comparing these training regimes in a diabetic model exists.

One aim of this work was to monitor the influence of the maternal environment before conception in an attempt to delineate the influence of this state on conception, gestation, and offspring outcome. During the period before mating, there was no significant difference in body weight or food consumption among the three groups. This finding differs from previous work in which exercise-trained diabetic animals had lower body weights (12, 13) and lower food intakes (12) than their control counterparts. It should be noted, however, that Goodyear et al. (13) ran the animals at a pace 10 m/min faster than the present study as well as at twice the daily duration (2 × 60-min sessions/day). The enhanced stress placed on these animals could have depressed their appetite, resulting in a decrease in food intake and a consequent decrease in body weight. Moreover, the mere fact that animals were physically removed from food for at least twice the total time per week could have impinged on their ability to consume the volume of food necessary, relative to their energy expenditure and relative to their control counterparts.

Moderate endurance exercise training before pregnancy had no effect on 2-h fasting plasma glucose concentration, insulin levels, or response to a glucose challenge. This lack of exercise effect has been reported previously in equally severely diabetic female animals (13, 26) and in more critically diabetic males (20). It appears that a minimal level of insulin is necessary for enhancements in glucose utilization to occur in response to training (11). Those studies that reported a positive effect of exercise training typically utilized animals with a lesser degree of hyperglycemia (6, 12).

### Table 3. Offspring blood parameters at death

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SS</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose, mmol/l</td>
<td>4.36 ± 0.33</td>
<td>4.41 ± 1.06</td>
</tr>
<tr>
<td>Insulin, ng/ml</td>
<td>4.00 ± 0.01</td>
<td>4.00 ± 0.01</td>
</tr>
<tr>
<td>Insulin-to-glucose ratio</td>
<td>0.01 ± 0.11</td>
<td>0.01 ± 0.11</td>
</tr>
<tr>
<td>Area under glucose clearance, mmol/l</td>
<td>1.06 ± 4.60</td>
<td>0.04 ± 0.04</td>
</tr>
<tr>
<td>Cholesterol, mg/dl</td>
<td>320.25 ± 43.72</td>
<td>320.25 ± 43.72</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SE. Offspring from nondiabetic control (C) pups born to foster dams, n = 20; EE, n = 17; SS, n = 14 animals. *P < 0.05 vs. EE pups, and †P < 0.05 compared with SS animals.

### Table 4. Tissue weights for offspring at death

<table>
<thead>
<tr>
<th>Tissue</th>
<th>SS</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>4.36 ± 0.33</td>
<td>4.41 ± 1.06</td>
</tr>
<tr>
<td>Heart</td>
<td>0.48 ± 0.01</td>
<td>0.36 ± 0.05</td>
</tr>
<tr>
<td>Soleus</td>
<td>0.04 ± 0.01</td>
<td>0.04 ± 0.01</td>
</tr>
<tr>
<td>Plantaris</td>
<td>0.08 ± 0.04</td>
<td>0.06 ± 0.04</td>
</tr>
<tr>
<td>Red gastrocnemius</td>
<td>0.20 ± 0.02*</td>
<td>0.13 ± 0.02</td>
</tr>
<tr>
<td>White gastrocnemius</td>
<td>0.23 ± 0.02</td>
<td>0.21 ± 0.03</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SE. Animals were killed at 28 days of age. C, n = 20; EE, n = 17; SS, n = 14 animals. *P < 0.05 vs. SS pups.
Litter size and offspring viability in EE animals were similar in the SS dams. Average litter size was slightly larger than that previously reported under diabetic conditions (4, 7, 23), and the percentage of viable offspring in the EE group was similar to that in studies without exercise perturbations (4, 7). Failure to continue exercise during gestation had a marked impact on the pregnancy outcome. All pups born to the ES dams died within 12 h after birth. Two of the three dams in the ES group delivered animals that were grossly malformed. In addition, one ES mother died during labor, after delivering severely abnormal offspring. It appears that the sudden perturbation in glucose and lipid homeostasis due to the cessation of exercise training coupled with the normal diabetogenic effects of pregnancy acted synergistically to negatively influence both the mother and the fetus. Because of the lack of gross abnormalities in the EE group, one could suggest that exercise may have provided a more “controlled” environment for the fetus that ultimately decreased its risk of dysmorphogenesis. These data must, however, be interpreted cautiously because of the low sample size in this study.

Previous studies have shown a “blunting” of the glucose tolerance curve during gestation in diabetic animals. Although the glucose challenge data were not significantly different among groups, EE and SS groups tended to have a more typical diabetic response in plasma glucose and area under the glucose curve. The diabetic condition appeared to worsen in the ES group. The ES offspring may have been bathed in a nutrient-rich medium, exposing them to the highly teratogenic conditions of hyperglycemia, hypertriglyceridemia, and ketosis (9, 18).

Although one might expect that the benefits of exercise training on glucose and lipid metabolism would not be completely eliminated over the short gestation period, it is possible that removal of the exercise stimulus in the ES group may have altered lipolytic activity in a fashion that made handling the pregnancy-induced hypertriglyceridemia more difficult instead of easier. Perturbations in lipid homeostasis during detraining (ES animals) could lead to a cascade of events, starting with increased free fatty acid oxidation and upregulated ketogenesis (via incomplete free fatty acid oxidation). A reflexive suppression in glucose uptake and oxidation coupled with increased gluconeogenesis through hepatic pathways could result in a markedly elevated glucose concentration during the detraining of the ES group. These perturbations in glucose and lipid homeostasis would alter the fuel mixture provided to the fetus and potentially negatively affect the offspring. The enhanced weight gain and food consumption that was observed in ES animals substantiate an inability to adjust to a sedentary level of caloric expenditure. Further research examining changes in lipid profile under these conditions is essential.

Offspring from diabetic mothers (EE and SS) had lower body weight at birth relative to that observed in pups from control animals (7, 16). The degree of microsomia evident in the diabetic offspring was similar to previous reports (1, 14, 16). As has been proposed by the “Pedersen hypothesis,” this low birth weight is a direct result of the hyperglycemic state of the mother. Placental transfer of high levels of glucose initially results in fetal hyperglycemia and reflexive hyperinsulinemia (22). As a consequence of this insulin hypersecretion, the developing beta cells in the offspring become exhausted and ultimately experience a reduction in their ability to secrete insulin. It is believed that this exhaustion of the beta cells is related to insensitivity to glucose rather than a shift in the glucose-insulin dose-response relationship (1, 2, 16). In utero, once the fetus becomes insensitive to glucose and is no longer able to secrete insulin, hypoinsulinism results and renders the offspring incapable of utilizing the enriched nutrient mix available. The ultimate result is a reduction in body weight or microsomia (14). Data from offspring of EE mothers in this study would support this hypothesis.

By 28 days of age, EE offspring experienced an accelerated growth phase and were now of similar body weight to those offspring from the control dams. One might speculate that the beta cells were not permanently damaged at the time of exhaustion and their insulin secretory ability was reflexively exaggerated throughout the maturation of the animal. Increased insulin would promote growth under conditions of adequate fuel resources. The hypoglycemic-hyperinsulinemic response of the 4-wk-old EE pups to a glucose challenge reflects this overcompensatory response.

Offspring from diabetic sedentary mothers had a hyperglycemic response to a glucose challenge and slightly depressed insulin levels at 4 wk of age. The pups appeared to be developing into adults similar to their mothers, with hyperglycemia and hypoinsulinemia typical of type I diabetes. This persistence of abnormal glucose homeostasis in adulthood, without the influence of genetics, has been previously reported by Gaugui et al. (10). These authors suggested that perturbations in the fetal environment in utero (hyperglycemia) contribute to the development of diabetes mellitus in adulthood (10). Results from the present work provide additional support for this hypothesis.

In summary, moderate exercise training before pregnancy in severely diabetic female rats did not improve oral glucose tolerance or hyperglycemia. The ability of these diabetic female rats to become pregnant was neither hindered nor facilitated by exercise training. Furthermore, continuation of exercise training during gestation did not appear to negatively affect pregnancy, as indicated by litter size, percentage of viable offspring, and a reversal in the normally observed hypoinsulinism and hyperglycemia at 28 days of age in diabetic offspring. In contrast, cessation of exercise in conjunction with initiation of pregnancy appears to perturb the level of glucose and lipid homeostasis established under diabetic exercise conditions in such a way as to negatively affect the response of the dams to pregnancy and pregnancy outcome. These data have relevance to long-term clinical application, whereby current trends that encourage exercise as an integral part of diabetic treatment and/or management must
more comprehensively define the implications of exercise training. Most importantly, we must define the influence of exercise cessation on numerous aspects of maternal and fetal outcomes. It can provide insights for clinical exercise recommendations before and during pregnancy for diabetic women.

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