ABSTRACT

Effects of melengestrol acetate on reproductive performance of 48 female rats and 20 of their female progeny were evaluated in two experiments. Treatments of 0, .01, and .1 mg in .1 ml of propylene glycol were given three groups of 16 rats for 7 days. From day 7 following sperm detection (10-day breeding period), half from each group received .1 mg per day for 14 days. Experiment 2 tested performance of 10 progeny exposed or unexposed to in utero treatment.

Cyclic changes in Experiment 1 were inhibited only in animals receiving daily initial treatment of .1 mg. Estrus was detected in 61.5% of animals within 48 h of treatment withdrawal. Synchronization caused no significant changes in conception rates or postbreeding results of treatment. Treatment during gestation lowered weight gain for dams, increased gestation length, and decreased number of pups per litter. Treatment lowered mean weight per litter and weight per pup. It also caused high mortality among pups.

In Experiment 2, there were no differences between progeny groups in gestation length, litter size, weight per litter, weight per pup, or mortality rate.

INTRODUCTION

Successful synchronization of estrus and ovulation with various synthetic progestational compounds have been reported in dairy cattle (3, 11), beef cattle (4, 12), and rats (5). Conception rates following breeding at the first synchronized estrus, however, have been generally low and variable (2, 6, 11). Weight gain and feed efficiency in heifers fed melengestrol acetate (MGA) have been improved (1, 7). Treatment of dams with MGA during gestation has resulted in a significantly lower calf birth weight but had no effect on gestation length or incidences of difficult calvings and still births (3, 8). Treating pregnant rats with MGA during gestation decreased litter size and litter weight (5). No data, however, are available on the future reproductive performance of the young exposed to MGA in utero.

Investigations were to determine synchronization of estrus, conception rates, and reproductive performance of rats treated with MGA prior to breeding and during gestation. In another experiment reproductive performance of female rats born to dams treated with MGA during gestation was investigated to determine any possible carry-over effects.

MATERIALS AND METHODS

Experiment 1

Forty-eight sexually mature Sprague-Dawley female rats (225 to 260 g body weight) were assigned randomly to three groups of 16 rats each. The animals were identified by ear notching and placed in cages, each cage containing four rats. Purina rat pellets and water were provided ad libitum. For two cycles prior to the initiation of the experiment, all rats were checked for normal cyclic changes twice daily at approximately 12-h intervals by the vaginal smear technique. Initial treatment for
synchronization of estrus consisted of daily single subcutaneous injections of .01 mg and .1 mg of crystalline MGA in .1 ml of propylene glycol for 7 consecutive days for two groups of animals. One group of animals serving as controls receiving injections of .1 ml of propylene glycol for the same duration. Treatments were initiated irrespective of stage of estrous cycle, and vaginal smears were continued until sperm were detected. Following withdrawal of initial treatment, the animals were placed in breeding cages with male rats, each cage containing four females and two male rats. A breeding period of 10 days was allowed. Each female was placed in an individual cage the day sperm were found in the vaginal smear (day 1 of pregnancy). Beginning on day 7 of pregnancy, one-half of the rats from each group including controls were daily injected with .1 mg of MGA in .1 ml of propylene glycol for 14 days. Based on results of initial treatment, this amount of MGA was chosen as the minimum effective daily dose to inhibit cyclic changes. Data on weight gain of dams during treatment, gestation length, litter size, litter weight, and mortality at birth were recorded. All data were analyzed by the factorial analysis of variance (9). Where no significant interactions occurred, sums of squares for interaction were added to the sums of squares for error in the error mean square.

Experiment 2

Treatment of dams with MGA during gestation resulted in a pronounced depressing effect on all measures of reproductive performance and resulted in a high mortality in the newborn pups. Although no gross abnormality was detected visually at birth, it was deemed necessary to raise some of the female pups from the control dams and those exposed to MGA treatment in utero and compare their reproductive performance to determine any possible carry-over effect of such treatment. Cyclic changes in vaginal cytology in the second generation females reaching sexual maturity were checked as before by the vaginal smear technique. Following completion of two cycles, 10 females from each group (mean body weight 260 g) were assigned at random to two groups. The females were identified by ear notching and put into breeding cages with males. A breeding period of 10 days was allowed as in the previous experiment. The day sperm were found in the vaginal smear was designated as day 1 of pregnancy, and the females were put in individual cages. Data on gestation length, litter size, litter weight, and mortality rate were recorded and analyzed as described before. The second generation females born to dams receiving no treatment during gestation were designated as controls and those born to treated dams as treated.

RESULTS AND DISCUSSION

Experiment 1

Cyclic changes in vaginal cytology were not altered in animals treated with propylene glycol or .01 mg of MGA in propylene glycol. Daily injections of .1 mg of MGA inhibited cyclic changes during the treatment period, and these animals were in estrus within 2 to 9 days following withdrawal of treatment. Estrus was detected in 61.5% of the MGA (.1 mg) treated animals in 48 h. Subcutaneous injections of .05 mg of MGA have been reported to be the minimum effective daily dose to inhibit cyclic changes in the rat, and such animals resumed cyclicity between 2 to 12 days following treatment withdrawal (5). No differences in conception rates of animals were significant among the different groups. However, conception rate was lowered following MGA treatment in dairy heifers (3) and rabbits (2).

No interactions were significant (P>.1) between pretreatment for estrus synchronization and postbreeding treatment indicating that pretreatment did not influence the effects of MGA given during gestation with regard to any of the characteristics. Therefore, all data were pooled into two groups, those that received pretreatment only and those that received both pre- and postbreeding treatments. Results are in Table 1.

The mean weight gain for animals receiving both initial and postbreeding treatments was less (P<.01) than that of animals receiving initial treatment only. In contrast, feeding MGA to cattle has had growth promoting effects (1, 7), and the depressing effect in the rat may relate to differences of species. Mean gestation length of animals receiving treatment

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TABLE 1. Mean weight gain and reproductive performance of female rats treated with MGA prior to breeding, during gestation, or at both times.a

<table>
<thead>
<tr>
<th>Item</th>
<th>Pretreatment</th>
<th>Prebreeding plus post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \bar{x} )</td>
<td>SE</td>
</tr>
<tr>
<td>Weight gain by dam (g)</td>
<td>50.9</td>
<td>.5</td>
</tr>
<tr>
<td>Gestation length (days)</td>
<td>21.9</td>
<td>.1</td>
</tr>
<tr>
<td>No. pups per litter</td>
<td>10.4</td>
<td>.4</td>
</tr>
<tr>
<td>Weight per litter (g)</td>
<td>73.6</td>
<td>2.8</td>
</tr>
<tr>
<td>Weight per pup (g)</td>
<td>7.1</td>
<td>.1</td>
</tr>
<tr>
<td>Percent mortality</td>
<td>2.1</td>
<td></td>
</tr>
</tbody>
</table>

aPretreatment consisted of daily sc injections of .00, .01, or .1 mg of MGA in .1 ml of propylene glycol for 7 days. Postbreeding treatment consisted of daily sc injections of .1 mg of MGA for 14 days starting on day 7 of gestation.

bOne animal receiving no postbreeding treatment had to be delivered by caesarean section at term. Although data regarding pups born in this manner were used for appropriate analyses, the data on gestation length for this particular animal was not included for statistical analysis.

*P<.05; **P<.01.

during gestation was longer (P<.01) than that of animals not receiving such treatment. In dairy heifers, however, gestation length was not increased due to feeding MGA during gestation even when continued through parturition (3, 8). We observed no difficulty in littering. Similar observations have been reported in dairy heifers (8) and in the bitch (10).

Postbreeding treatment with MGA lowered mean litter size (P<.05) and mean litter weight (P<.01). Although mean litter size was significantly smaller, the mean weight per pup from such dams (Table 1) was also lower (P<.01) than that of animals not receiving MGA treatment during gestation. In addition, although visual observation did not reveal any gross abnormalities and all pups were carried to term, postbreeding treatment resulted in a high percentage of pup mortality. These findings agree with (5). A significant reduction in calf birth weight following MGA treatment has been reported (8). In contrast, treatment of pregnant bitches with MGA resulted in a slightly higher birth weight in pups (10). Visual observation in the rat (5) and both visual and histopathological observations in dairy cattle (8) have failed to indicate any abnormalities due to MGA treatment which could account for a high mortality rate in newborn pups.

Experiment 2

Three second generation females from the

TABLE 2. Mean reproductive performance of second generation female rats born to dams with or without MGA treatment during gestation.

<table>
<thead>
<tr>
<th>Item</th>
<th>Control b</th>
<th>Treated b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \bar{x} )</td>
<td>SE</td>
</tr>
<tr>
<td>Gestation length (days)</td>
<td>22.8</td>
<td>.1</td>
</tr>
<tr>
<td>No. pups per litter</td>
<td>9.0</td>
<td>.9</td>
</tr>
<tr>
<td>Weight per litter (g)</td>
<td>66.5</td>
<td>7.0</td>
</tr>
<tr>
<td>Weight per pup (g)</td>
<td>7.4</td>
<td>.1</td>
</tr>
<tr>
<td>Percent mortality</td>
<td>.0</td>
<td></td>
</tr>
</tbody>
</table>

aFemales born to dams receiving no MGA treatment during gestation are designated as control.
bFemales born to dams receiving MGA treatment during gestation are designated as treated.
control dams and one from the treated dams did not conceive in a breeding period of 10 days. Results of this experiment are in Table 2. There were no differences in the mean gestation length or the number of pups per litter (P>.1). The mean litter weight and weight per pup were similar in both groups. There was no mortality among pups born to the second generation control females and only 2.5% among the pups born to females exposed to MGA treatment in utero.

**DISCUSSION**

These experiments have revealed a few observations not reported earlier. A dose of MGA capable of suppressing estrous cyclicity in the rat apparently does not affect conception rates of first estrus following withdrawal of such treatment. A high mortality rate among newborn pups exposed to MGA treatment in utero was a surprising finding as no gross abnormalities were observed. A high mortality rate, however, may appear reasonable as low birth weight is generally indicative of less vigor and survival ability. It has been reported that MGA was 300 to 900 times as potent as medroxy-progesterone (MAP) when given orally to cattle but only 10 to 15 times as potent in inhibiting estrus when given by intravenous injection (12). Perhaps rumen microorganisms convert MGA to a more active compound. It is also possible that in its unaltered form, MGA may be responsible for the reduced weight gain in dams and high mortality rate in newborn pups. The mortality rate may be related to delayed lactation in the MGA treated dams. No such observation, however, has been made in dairy cattle (3). Also, most of the pups constituting the mortality rate in the present experiment died within the 1st day of littering. However, the results from the second experiment indicate that there were no detrimental carry-over effects on the subsequent reproductive performance of the females exposed to MGA treatment in utero.

**ACKNOWLEDGMENT**

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**REFERENCES**