Spray-dried plasma attenuates inflammation and improves pregnancy rate of mated female mice

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ABSTRACT: Three studies were conducted to test the hypothesis that dietary spray-dried plasma (SDP) might improve pregnancy rate by ameliorating inflammation, using mice in an experimental model that produces a low pregnancy rate. Mated female mice (C57BL/6 strain) were purchased and shipped from a vendor (Bar Harbor, ME) to the university facility (Urbana, IL) on the day the vaginal plug was found (gestation day [GD] 1), arriving at the laboratory on GD 3 after 2 d transport by air and ground. Mice (Exp. 1: \( n = 250, 16.0 \pm 1.2 \) g BW; Exp. 2: \( n = 202, 16.2 \pm 1.2 \) g BW; Exp. 3: \( n = 156, 16.4 \pm 1.1 \) g BW) were housed in individual cages and randomly assigned to dietary treatments (Exp. 1: 0 [CON] and 8% SDP in the diet, ≥ 90 mice/diet; Exp. 2: 0, 1, 2, 4, and 8% SDP in the diet, ≥ 40 mice/diet; Exp. 3: 0, 1, and 8% SDP in the diet, 48 mice/diet) fed from arrival. In Exp. 1 and 2, pregnancy of each mouse was determined on GD 17 based on BW, shape of abdomen, and inspection postmortem, and maternal growth performance from GD 3 to 17 was measured. On GD 19, pregnant mice in Exp. 2 were euthanized to measure number of fetuses and fetal and placental weights. Pregnancy rates in CON were low in both Exp. 1 (11%) and Exp. 2 (7%). The SDP consistently and markedly increased \((P < 0.05)\) pregnancy rates in both Exp. 1 (49%) and Exp. 2 (35–43%) compared with the CON. In Exp. 3, 12 randomly selected mice were euthanized immediately after they arrived as an initial group. From GD 4 to 7, randomly selected mice were also euthanized each day (12 mice/diet). After euthanasia, the abdominal cavity was opened to check pregnancy by uterine inspection and to collect blood and uterus samples for immune measurements. The SDP increased \((P < 0.05; 40 \text{ vs. } 15\%)\) pregnancy rate compared with the CON. Concentrations of indicators of inflammation and stress (uterine TNF-α and IFN-γ, and serum TNF-α, C-reactive protein, and cortisol) were greatest \((P < 0.05)\) and an anti-inflammatory cytokine (TGF-β1) was lowest \((P < 0.05)\) soon after arrival, on GD 3 or 4. The SDP decreased \((P < 0.05)\) the uterine concentrations of TNF-α and IFN-γ, and serum TNF-α, C-reactive protein, and cortisol, compared with the CON, but increased \((P < 0.05)\) the uterine concentration of TGF-β1. In conclusion, dietary SDP improves the low pregnancy rates in this model, apparently by attenuating inflammation.

Key words: immune responses, mated female mice, pregnancy rate, reproductive performance, spray-dried plasma


INTRODUCTION

Spray-dried plasma (SDP) is a complex mixture of many physiological components including immunoglobulins, glycoproteins, growth factors, and others (Coffey and Cromwell, 2001; Moretó and Pérez-Bosque, 2009) and provides anti-bacterial effects (Nollet et al., 1999; Niewold, 2007), anti-inflammatory effects (Pérez-Bosque et al., 2004; Pettigrew et al., 2006; Peace et al., 2011), improvement of intestinal barrier function (Pérez-Bosque et al., 2006;
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Evidence in mice and humans indicates that inflammation interferes with maintenance of pregnancy (Rivera et al., 1998; Laird et al., 2003; Salmon, 2004), fetal survival and growth (Rivera et al., 1998) and implantation of embryos (Erlebacher et al., 2004; Salmon, 2004). Feeding SDP to sows in some situations produces modest improvements in reproductive performance (Crenshaw et al., 2007, 2008; Fruge et al., 2009), perhaps because it reduces inflammation. We initiated studies to test the hypothesis that feeding SDP to pregnant mice for 2 wk would protect against the detrimental effects of experimentally-stimulated inflammation during late pregnancy. We used C57BL/6 mice, known for poorer reproductive performance than outbred mice, shipped from the vendor on the day after mating. Few (17%) of the mice fed the control diet were found to be pregnant, but a higher proportion (67%) of those fed SDP were pregnant.

The objectives of the present study were 1) to determine whether the apparent beneficial effects of SDP on pregnancy are repeatable in a larger experiment; 2) to establish the lowest dietary concentration of SDP necessary to get the improvement of pregnancy rates; and 3) to test the hypothesis that feeding SDP soon after mating reduces inflammation and improves reproductive success.

MATERIALS AND METHODS

The protocol for these experiments were reviewed and approved by the Institutional Animal Care and Use Committee of the University of Illinois at Urbana-Champaign. The experiments were conducted in the mouse facility of the Institute for Genomic Biology building at the University of Illinois at Urbana-Champaign.

Animals, Housing, Diets, and Experimental Design

Mated female mice (C57BL/6 strain) were shipped from a vendor (The Jackson Laboratory, Bar Harbor, ME) to the university facility (Urbana, IL) on the day the vaginal plug was found (gestation day [GD] 1), arriving at the IL facility on GD 3 after 2 d transport by air and ground. When the mice arrived at the facility, each mouse was weighed and housed in an individual cage with a feeder, a waterer, and bedding and with controlled temperature (23°C), humidity (40%), and a 12 h light and dark cycle. They were immediately and randomly assigned to dietary treatments and allowed free access to feed and water during the experimental period. The diets were formulated to meet or exceed NRC (NRC, 1995) estimates of nutrient requirements of pregnant mice and to have similar metabolizable energy, crude protein, and amino acids levels, and no antibiotics (Table 1). The diets were pelleted without heating (cold-pelleted) using a pellet press. The SDP was produced from bovine blood (AP 920; APC, Inc., Ankeny, IA).

<table>
<thead>
<tr>
<th>Item</th>
<th>CON</th>
<th>SDP1</th>
<th>SDP2</th>
<th>SDP4</th>
<th>SDP8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingredient, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>25.58</td>
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<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
</tr>
<tr>
<td>Spray-dried plasma</td>
<td>–</td>
<td>1.00</td>
<td>2.00</td>
<td>4.00</td>
<td>8.00</td>
</tr>
<tr>
<td>Soybean oil</td>
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<td>7.00</td>
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<tr>
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<td>5.00</td>
<td>5.00</td>
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<tr>
<td>AIN-93 MX³</td>
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<td>3.50</td>
<td>3.50</td>
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</tr>
<tr>
<td>AIN-93 VX⁴</td>
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<td>1.00</td>
<td>1.00</td>
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</tr>
<tr>
<td>DL-methionine</td>
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<td>0.26</td>
<td>0.27</td>
<td>0.29</td>
<td>0.32</td>
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<tr>
<td>Choline bitartrate</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
</tr>
</tbody>
</table>

1 CON = control diet; SDP1 = 1% spray-dried plasma diet; SDP2 = 2% spray-dried plasma diet; SDP4 = 4% spray-dried plasma diet; SDP8 = 8% spray-dried plasma diet.
2 The SDP was produced from bovine blood (AP 920; APC, Inc., Ankeny, IA).
3 Dyets, Inc., Bethlehem, PA. Provided as milligrams per kilogram of diet: calcium, 5,000; phosphorus, 1,561; potassium, 3,600; sodium, 1,019; chloride, 1,571; sulfur, 300; magnesium, 507; iron, 35; copper, 6; manganese, 10; zinc, 30; chromium, 1; iodine, 0.2; selenium, 0.15; fluorine, 1; cobalt, 0.5; molybdenum, 0.15; silicon, 5; nickel, 0.5; lithium, 0.1; vanadium, 0.1.
4 Dyets, Inc., Bethlehem, PA. Provided per kilogram of diet: thiamin HCl, 6 mg; riboflavin, 6 mg; pyridoxine HCL, 7 mg; niacin, 30 mg; calcium pantothenate, 16 mg; folic acid, 2 mg; biotin, 0.2 mg; cyanocobalamin (vitamin B12), 25 mg; vitamin A palmitate, 4,000 IU; vitamin E acetate, 75 IU; vitamin D₃, 1,000 IU; vitamin K₁, 0.75 mg.
On GD 17, pregnancy of the mice was determined on the basis of their BW and shape of abdomen (normal abdomen of nonpregnant mice vs. full, bulgy, rough, or bumpy abdomen of pregnant mice), and was confirmed later by inspection postmortem. Measurements were pregnancy rate, expressed as a percent (%) of those assigned to each treatment, and growth performance of pregnant mice from GD 3 to GD17 (ADG, ADFI, and G:F).

**Experiment 2: Pregnancy, Maternal Growth Rate, and Reproductive Performance**

A total of 202 mated female mice (16.2 ± 1.2 g BW; 1 group) were used and dietary treatments were 0, 1, 2, 4, or 8% SDP in the diet (CON, SDP1, SDP2, SDP4, and SDP8, respectively). The levels of SDP (1, 2, 4, and 8%) in the diet were chosen based on the results from the Exp. 1 and on previous studies with lactating sows (Crenshaw et al., 2007, 2008; Fruge et al., 2009). The total numbers of mated female mice were 42, 40, 40, 40, and 40 in the CON, SDP1, SDP2, SDP4, and SDP8, respectively. The CON and SDP8 were the same dietary treatments in both Exp. 1 and 2.

Reproductive and growth performances were measured as described in Exp. 1. The pregnant mice were euthanized by cervical dislocation under CO₂ anesthesia on GD 19. The total number of fetuses was recorded and then the fetuses and placentas were collected and weighed. The average fetal to placental weight ratio was calculated.

**Experiment 3: Pregnancy Rate and Immune and Stress Indicators**

A total of 156 mated female mice (16.4 ± 1.1 g BW; 1 group) were used and dietary treatments were 0, 1, or 8% SDP in the diet (CON, SDP1, and SDP8, respectively). The levels of SDP (1 and 8%) in the diet were chosen based on the results from the Exp. 1 and 2. As an initial group, 12 randomly selected mice were weighed and euthanized by CO₂ immediately after they arrived at our facility on GD 3. The rest of the mice were also weighed and euthanized by CO₂; 12 mice per dietary treatment each day from GD 4 to 7. After euthanasia, the abdominal cavity was opened to weigh and euthanized by CO₂ immediately after were chosen based on the results from Exp. 1 and weight ratio was calculated.

The collected blood samples (approximately 500 µL of whole blood) were allowed to clot at room temperature for 2 h, kept at 4°C overnight, and then centrifuged for 10 min at 2,000 × g at room temperature. The serum was collected and stored at −80°C until measurements were conducted. The uteri were frozen in liquid nitrogen and then stored at −80°C until processing based on the report by Robertson et al. (2006). The frozen uteri were weighed, chopped by scissors, and placed in conical tubes, and then cold dissolved protease inhibitor (Roche Diagnostics, Indianapolis, IN) in PBS was added. The samples were homogenized for 45 s using a high-speed homogenizer (Fisher Scientific, Pittsburgh, PA), and thawed on ice. The samples were centrifuged at 10,000 × g for 20 min at 4°C, and supernatants were collected and stored at −80°C until measurements were conducted. Cytokines, C-reactive protein (CRP), and cortisol were measured in the uterine homogenates or the serum using mouse ELISA kits following the manufacturer’s procedure (tumor necrosis factor-α [TNF-α, Invitrogen Corporation, Grand Island, NY]; interferon-γ [IFN-γ, R&D systems, Minneapolis, MN]; transforming growth factor-β1 [TGF-β1, R&D systems, Minneapolis, MN]; cortisol [TSZ ELISA, Waltham, MA]; C-reactive protein [GenWay Biotech, Inc., San Diego, CA]). In addition, total protein (TP) of the uterine homogenates was measured using Bradford’s reagent and bovine serum albumin as standard following the manufacturer’s procedure (Bio-Rad Laboratories, Hercules, CA) and the data were used to normalize the uterine cytokine concentrations. A standard curve was included in each assay plate for cytokines, CRP, cortisol, and TP. Results were measured using a microplate reader (Dynex Technologies, Chantilly, VA). All the cytokine measurements of gestational tissue and serum samples were based on the report of Robertson et al. (2006). The intra-assay coefficients of variation for TNF-α, IFN-γ, TGF-β1, CRP, and cortisol were 5.9, 4.9, 3.4, 4.3, and 6.6%, respectively. The inter-assay coefficients of variation for TNF-α, IFN-γ, TGF-β1, CRP, and cortisol were 8.7, 8.3, 8.4, 8.9, and 8.6%, respectively.

**Statistical Analyses**

Data were analyzed as a completely randomized design. For pregnancy rate in Exp. 1, 2, and 3, the experimental unit was the mated female mouse and data were analyzed by the χ² test. There was no effect of groups in Exp. 1 so that term was excluded from the model. For other measurements in Exp. 1 and 2, the experimental unit was the pregnant mouse or litter and data were analyzed by the PROC GLM procedure of SAS (SAS Inst. Inc., Cary, NC). The statistical model included effects of diet. In addition, linear and quadratic effects of SDP level were tested in Exp. 2, us-
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For other measurements in Exp. 3, the experimental unit was the mouse and data were analyzed by the PROC GLM procedure of SAS (SAS Inst. Inc.). The statistical model included effects of diet, time, and their interaction. In addition, pair-wise comparisons were performed among dietary treatments when a main effect of diet was found. Results are given as means ± SE. Statistical significance and tendency were considered at \( P < 0.05 \) and 0.05 ≤ \( P < 0.10 \), respectively.

**RESULTS**

**Experiments 1 and 2: Pregnancy, Maternal Growth Rate, and Reproductive Performance**

The pregnancy rate of mated female mice fed the CON was low in both Exp. 1 (overall 11%; Fig. 1A) and Exp. 2 (7%; Fig. 1B). All SDP treatments, regardless of levels, consistently and markedly increased \( P < 0.05 \) pregnancy rates in both Exp. 1 (overall 49%; Fig. 1A)
and Exp. 2 (35 to 43%; Fig. 1B) compared with the CON. No differences in pregnancy rates were found among treatments containing SDP in Exp. 2 (Fig. 1B).

The SDP diet increased \((P < 0.05)\) ADG and G:F of pregnant mice in Exp. 1 compared with the CON (Table 2). Similarly, the SDP linearly increased \((P < 0.05)\) ADG and G:F of pregnant mice in Exp. 2 compared with the CON, as the level of SDP in the diet was increased (Table 2). No effect of diet was found for ADFI in either experiment (Table 2).

In Exp. 2, the number of fetuses increased \((P < 0.05)\) linearly as the level of SDP in the diet was increased (Table 3). Fetal weight tended to increase quadratically \((P = 0.069)\) and the fetal to placental weight ratio tended to increase linearly \((P = 0.055)\) as the level of SDP in the diet was increased (Table 3). No effect of diet was found for placental weight (Table 3).

Table 2. Growth performance of pregnant mice

<table>
<thead>
<tr>
<th>Item</th>
<th>Exp. 1</th>
<th>Exp. 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CON</td>
<td>SDP1</td>
</tr>
<tr>
<td>Pregnant mice, n</td>
<td>17</td>
<td>–</td>
</tr>
<tr>
<td>ADG, g/d</td>
<td>0.64 ± 0.02</td>
<td>–</td>
</tr>
<tr>
<td>ADFI, g/d</td>
<td>3.17 ± 0.05</td>
<td>–</td>
</tr>
<tr>
<td>G:F, g/g</td>
<td>0.202 ± 0.006</td>
<td>–</td>
</tr>
</tbody>
</table>

1Values are means ± SE.
2CON = control diet; SDP1 = 1% spray-dried plasma diet; SDP2 = 2% spray-dried plasma diet; SDP4 = 4% spray-dried plasma diet; SDP8 = 8% spray-dried plasma diet.
3Diet = diet effect; Linear = linear effect of SDP level; Quadratic = quadratic effect of SDP level.
4A total of 9 mice were excluded because they began delivery before terminal data were collected.

Experiment 3: Pregnancy Rate and Immune and Stress Indicators

Few (15%; Fig. 1C) of the mated female mice fed the CON established pregnancy. Both SDP treatments markedly increased \((P < 0.05)\) overall pregnancy rates compared with the CON on GD 4 through GD 6 (overall 40%; Fig. 1C). This SDP effect on pregnancy rate was shown as early as 1 d after introduction of SDP in the diet (Fig. 1C). There was no difference in pregnancy rate between SDP1 and SDP8 (Fig. 1C).

The concentrations of pro-inflammatory cytokines, TNF-α (Fig. 2A) and IFN-γ (Fig. 2B), were highest on GD 3 and then decreased to GD 7 (Time, \(P < 0.05\)), but the concentration of an anti-inflammatory cytokine, TGF-β1 (Fig. 2C), was lowest on GD 3 or GD 4 and then increased over time (Time, \(P < 0.05\)). Either SDP1 or SDP8, or both SDP treatments decreased \((P < 0.05)\) the concentrations of the pro-inflammatory cytokines on GD 4 through GD 6 and increased \((P < 0.05)\) the concentration of the anti-inflammatory cytokine (Fig. 2C) on GD 4 through GD 7, compared

Table 3. Fetal and placental weights (wt) from pregnant mice (Exp. 2)

<table>
<thead>
<tr>
<th>Item</th>
<th>Exp. 1</th>
<th>Exp. 2</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>CON</td>
<td>SDP1</td>
</tr>
<tr>
<td>Pregnant mice, n</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Number of fetuses/litter</td>
<td>5.6 ± 0.5</td>
<td>5.6 ± 0.4</td>
</tr>
<tr>
<td>Average fetal wt, g</td>
<td>0.87 ± 0.04</td>
<td>1.04 ± 0.03</td>
</tr>
<tr>
<td>Average placental wt, g</td>
<td>0.101 ± 0.004</td>
<td>0.100 ± 0.003</td>
</tr>
<tr>
<td>Ratio, g/g</td>
<td>8.62 ± 0.66</td>
<td>10.66 ± 0.50</td>
</tr>
</tbody>
</table>

1Values are means ± SE.
2CON = control diet; SDP1 = 1% spray-dried plasma diet; SDP2 = 2% spray-dried plasma diet; SDP4 = 4% spray-dried plasma diet; SDP8 = 8% spray-dried plasma diet.
3Diet = diet effect; Linear = linear effect of SDP level; Quadratic = quadratic effect of SDP level.
4A total of 9 mice were excluded because they began delivery before terminal data were collected.
5Ratio = fetal weight divided by placental weight.
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with the CON. There was no difference in uterine cytokines between SDP1 and SDP8 (Fig. 2).

Serum concentrations of TNF-α as a pro-inflammatory cytokine (Fig. 3A), CRP as an indicator of inflammation (Fig. 3B), and cortisol as a stress indicator (Fig. 3C) were highest on GD 3 or GD 4 and then decreased (Time, \( P < 0.05 \)). Either SDP1 or SDP8, or both SDP treatments decreased \( (P < 0.05) \) all 3 of these concentrations at some time points compared with the CON (Fig. 3). There was no difference in serum immune and stress indicators between SDP1 and SDP8 (Fig. 3).

**DISCUSSION**

The present results confirm that feeding diets containing SDP can improve reproductive performance substantially under some conditions. Specifically, inclusion of SDP in the diet sharply increased the pregnancy rate of mice in these experiments, an effect that was clear after feeding SDP for only 24 h. We suggest that the improvement is mediated through the established anti-inflammatory effects of SDP (Pérez-Bosque et al., 2008; Maijó et al., 2012a,b). The implications of this observation for swine production are speculative, but the present results suggest that feeding SDP to sows experiencing inflammation during the postmating period may improve farrowing rates. Feeding SDP to sows during lactation has been shown to improve subsequent farrowing rate (Crenshaw et al., 2007, 2008), but feeding it from d 28 of pregnancy after implantation to farrowing did not improve farrowing rate (Crenshaw et al., 2010). We are not aware of studies that fed SDP to sows during the immediate postmating period, which would correspond to the timing in the present studies with mice. Perhaps feeding SDP improves reproductive success only in the presence of significant inflammation. In practice, the finding that a level of plasma as low as 1% of the diet is nearly as effective as higher levels is very important. However, the pregnancy rate on GD 7, the last day of sampling, was unexpectedly low and unaffected by SDP. Perhaps the daily manipulation of these mice for behavior observations (not described here) interfered with reproductive success.

The present studies confirm that this experimental model produced consistently low pregnancy rates in mice fed the CON, as our preliminary studies showed. The very low pregnancy rate as early as GD 4, about the time of implantation, indicates a failure to establish pregnancy rather than abortion. The present studies do not identify the components of the model that are most important but we suggest that transport stress is a likely key, in agreement with reports of pregnancy loss caused by transport stress from previous studies using farm animals (Dalin et al., 1988; Rojanasthien and Einarsson, 1988; Merrill et al., 2007). The importance of other components of the model, such as the strain or age of mice used, is unclear.

Under the conditions of the present studies, feeding SDP decreased uterine TNF-α and IFN-γ and serum TNF-α, CRP, and cortisol, but increased uterine TGF-β1. The lowest dose of SDP tested, 1% of the diet, was nearly as effective as higher doses. This indicates that SDP treatments attenuated the inflammation experienced by the mice fed CON. This observation agrees with the previously observed anti-inflammatory effects of SDP, including local and systemic alterations in pro- and anti-inflammatory cytokines, their mRNA expressions, and populations of immune cells (Touchette et al., 2002; Frank et al., 2003; Pettigrew, 2006). These observations collectively suggest that SDP reduces inflammation, and that in turn allows establishment of pregnancy.
The highest concentrations of uterine TNF-α and IFN-γ and serum TNF-α, CRP, and cortisol and the lowest concentration of uterine TGF-β1 occurred on GD 3 or 4, on arrival or soon thereafter. These data do not indicate whether this inflammatory state was caused by mating, by the long-distance transport, or by other factors. Previous literature shows various stressors can cause imbalance between pro- and anti-inflammatory responses by increasing production of pro-inflammatory cytokines locally and systemically (Arck et al., 2001; Cohen et al., 2001; Christian, 2012), resulting in inflammation, and that inflammation can interfere with normal reproduction in animals and humans (Rivera et al., 1998; Laird et al., 2003; Salmon, 2004). Notably, transport stress is detrimental to animal and human reproductive outcomes (Liptrap, 1993; ACOGC, 2001; Einarsson et al., 2008). Therefore, the beneficial effect of SDP on early-term pregnancy rate in the present studies may be through its anti-inflammatory effects described by several studies (Pérez-Bosque et al., 2010; Maijó et al., 2012a,b), resulting in the increased early-term pregnancy rate of mated female mice.

Growth rate of pregnant mice fed SDP was increased in the present studies. The greater number of fetuses may account for at least some of the difference in growth rate, but several reviews of studies with young pigs have shown a clear increase in growth rate when SDP was fed (Coffey and Cromwell, 2001; van Dijk et al., 2001; Pettigrew, 2006). Interestingly, when feed intake of pigs fed diets with SDP was under a pair-fed controlled intake to the level of control pigs, protein conversion efficiency was improved by about 18% (Jiang et al., 2000). The increased growth rate in the present studies was apparently driven by improved feed efficiency (G:F).

Overall, dietary SDP attenuates inflammatory immune responses of mated female mice, and this attenuation apparently contributed in the present study to a sharp increase in pregnancy rate. The lowest dose of SDP tested, 1% of the diet, was nearly as effective as higher doses.

**LITERATURE CITED**


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