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Original Research Article

# Dietary pectic oligosaccharide supplementation improves rat reproductive performance via regulating intestinal volatile fatty acids during middle gestation

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ABSTRACT

As a kind of green additive, pectic oligosaccharide (POS) may regulate some physiological functions of animals, such as gut health, antioxidant capacity, immunity and lipid metabolism. This study aimed to identify whether POS administration can improve maternal reproduction, and to determine the possible metabolism. A total of 48 pregnant Wistar rats randomly allotted into 2 groups, and each group was fed a diet supplemented with 0 or 800 mg/kg of POS. Pectic oligosaccharide administration increased rat born number ($P < 0.05$), did not affect rat embryo number on d 7 of gestation, but increased rat fetus number on d 14 of gestation ($P < 0.05$). On d 14 of gestation, POS treatment improved *Lactobacillus* and *Bifidobacterium* populations and volatile fatty acid concentrations of cecal digesta ($P < 0.05$), hormone (progesterone and nitric oxide) and cytokine (interleukin 2) concentrations of serum ($P < 0.05$), and antioxidant capacity of serum (increased total antioxidant capacity and decreased malondialdehyde) and placenta (increased total superoxide dismutase, decreased malondialdehyde) ($P < 0.05$) in pregnant rats. These results suggest that POS administration improved rat reproduction via decreasing fetus loss in middle gestation. This was due to the increased volatile fatty acid concentrations in rat gut improving hormone and inflammatory-cytokine productions, and antioxidant capacity.



## 1. Introduction

Functional oligosaccharides are used as a kind of green additive in food and feed. Functional oligosaccharides can maintain and promote growth and health of humans and animals, which may be due to their regulation effects on some physiological functions, such as glucose and lipid metabolism, gut microbiota, immunity, redox status, hematopoiesis, antitumor, and anti-pathogens (Delzenne and Kok, 2001; Ngo et al., 2008; Valcheva et al., 2009; Kawasaki et al., 2013; Xiong et al., 2015). Many studies showed that some functional oligosaccharides, including xylo-oligosaccharide, chito-oligosaccharide, mannan-oligosaccharide, galacto-mannan-oligosaccharide, have the capacity of increasing reproductive performance of animals, which could be due to the improved antioxidant capacity and immunity (Cheng et al., 2015; Guo et al., 2015; Duan et al., 2016; Wan et al., 2016).

As a functional oligosaccharide, pectic oligosaccharide (POS) is composed of pectic disaccharide and trisaccharide that contain galacturonic acid. The previous studies showed that citrus or hawthorn POS administration regulated lipid metabolism and

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antioxidant capacity in mice, and sugar beet POS treatment improved the gut microbiota derived from humans in an in vitro experiment (Fanaro et al., 2005; Kang et al., 2009; Li et al., 2010). Furthermore, we found that dietary apple POS supplementation improved growth performance, antioxidant capacity, immunity, gut microbiota, and gut health in weaned rats and piglets, efficiently alleviated the negative effect of rotavirus on piglets, and regulated lipid metabolism and deposition in finishing pigs (Mao et al., 2016a, 2017a, 2017b, 2019a; Chen et al., 2017). However, there are few studies on the regulation effects of POS administration on the reproductive performance.

It is well-known that the intake of nutrients and functional additives affects the reproductive performance of humans and animals during gestation. Our previous study showed that POS treatment can increase the reproduction in sows (data not published). Therefore, the aim of this study was to further verify the hypothesis that dietary POS supplementation could increase the reproductive performance of pregnant rats and to determine the possible mechanism.

## 2. Materials and methods

All experiments in this study were strictly conducted according to Chinese guidelines for animal welfare. All animal procedures were performed in accordance with the Guidelines for Care and Use of Laboratory Animals of Sichuan Agricultural University, and approved by the Animal Ethics Committee of Sichuan Agricultural University (Chengdu, China).

### 2.1. Animals and diets

A total of 60 female virgin Wistar rats weighed 250 to 270 g were obtained from Chengdu Dashuo Experimental Animal Co., Ltd. (Chengdu, China). All rats were individually housed in a temperature-controlled room (22 to 26 °C) on a 12L:12D photoperiod. After observing the estrous cycle of each rat, pregnancy was induced by overnight caging of a female in proestrus with a male with proven fertility. In the morning of the next day, the presence of spermatozoa in the vaginal smear was defined as pregnancy (d 1). Then, 48 pregnant rats in this pool were chosen randomly for the following 3 experiments.

### 2.2. Experimental design, parturition record and sample collection

In Exp 1, 16 pregnant rats were randomly allotted to 2 groups. The rats were fed diets supplemented with 0 or 800 mg/kg of POS from d 1 of pregnancy to delivery ($n = 8$). The number of rat pups born and born alive and the birth weight were recorded.

In Exp 2., 18 pregnant rats were fed 2 test diets from d 1 to the morning of d 7 ($n = 9$).The feed intake was recorded. On d 7, after being weighed, the rats were anesthetized with sodium pentobarbital, and the abdomen was cut open. The number of embryos was recorded. Then, the utero was quickly isolated and weighed.

In Exp 3., 14 pregnant rats were fed the diets supplemented with 0 or 800 mg/kg of POS from d 1 to the morning of d 14 ($n = 7$). On d 14, after being weighed, all rats were anesthetized with sodium pentobarbital, and the abdomen was exposed. The number of fetus was recorded. The utero was quickly isolated and weighed. The feed intake of rats was also recorded. After blood from abdominal aorta was collected, serum samples were made by centrifuging blood at 3,500 × *g* for 10 min, and stored at −20 °C. Then, the placenta and the cecal digesta were collected, immediately frozen in liquid nitrogen, and stored at −80 °C.

### 2.3. Analysis of microflora and volatile fatty acids (VFA) in cecal digesta

The bacterial DNA in the frozen cecal digesta was isolated by using a Stool DNA Kit (Omega BioTek, Doraville, CA) according to the manufacturer's instructions. The real-time quantitative PCR was carried out as described previously (Mao et al., 2016b). The primers and probes listed in Table 1 were obtained from TaKaRa Biotechnology (Dalian) Co., Ltd. (Dalian, China). Moreover, bacterial copies were transformed ($\log_{10}$) before statistical analysis.

The VFA including acetic acid, propionic acid and butyric acid concentrations were determined with a Varian CP-3800 gas chromatograph (Agilent Technologies, Santa Clara, CA) as described previously (Mao et al., 2019b).

### 2.4. Analysis of serum progesterone, estradiol, nitric oxide and vascular endothelial growth factor

Serum progesterone, estradiol and vascular endothelial growth factor (VEGF) concentrations were analyzed with a commercially available rat enzyme-linked immunosorbent assay (ELISA) kit (Xinle Co. Ltd., Shanghai, China) according to the manufacturer's instructions. Serum nitric oxide (NO) concentration was measured with an assay kit (Nanjing Jiancheng Bioengineering Institute, Nanjing, China) according to the manufacturer's instructions.

### 2.5. Analysis of serum cytokine

Serum interleukin (IL)-2, IL-6, IL-10 and interferon-γ (IFN-γ) levels were analyzed with a commercially available rat ELISA kit (Xinle Co. Ltd., Shanghai, China) according to the manufacturer's instructions.

### 2.6. Analysis of the antioxidant capacity in serum and placenta

The activities of total superoxide dismutase (T-SOD) and glutathione peroxidase (GSH-Px), total antioxidant capacity (T-AOC), and malondialdehyde (MDA) concentrations in serum and placenta were determined by using commercial kits purchased from Nanjing Jiancheng Bioengineering Institute (Nanjing, China) according to the manufacturer's instructions.

### 2.7. Statistical analysis

All data were processed with Microsoft Excel 2013, and analyzed using the unpaired *t* test of SAS (version 8.1, SAS Institute, Gary, NC). Results were expressed as means ± standard errors (SE). $P < 0.05$ was considered a statistical significance, and $P < 0.10$ was deemed a statistical tendency.

**Table 1**
Primers and probes for real time quantitative PCR.

| Bacteria | Primer | Nucleotide sequences 5′-3′ |
|---|---|---|
| *Escherichia coli* | Forward | CATGCCGCGTGTATGAAGAA |
| | Reverse | CGGGTAACGTCAATGAGCAAA |
| | probe | AGGTATTAACTTTACTCCCTTCCTC |
| *Bifidobacterium* | Forward | CGCGTCCGGTGTGAAAG |
| | Reverse | CTTCCCGATATCTACACATTCCA |
| | probe | ATTCCACCGTTACACCGGGAA |
| *Lactobacillus* | Forward | GAGGCAGCAGTAGGGAATCTTC |
| | Reverse | CAACAGTTACTCTGACACCCGTTCTTC |
| | probe | AAGAAGGGTTTCGGCTCGTAAAACTCTGTT |
| Total bacteria | Forward | ACTCCTACGGGAGGCAGCAG |
| | Reverse | ATTACCGCGGCTGCTGG |

## 3. Results

### 3.1. Reproductive performance of pregnant rats (Exp. 1)

As shown in Table 2, dietary POS supplementation enhanced the number of rat pups born and born alive per litter by 16.35% and 17.64%, respectively ($P < 0.05$). Compared with the CON group, POS treatment did not influence birth weight and average birth weight of rat pups born alive per litter.

**Table 2**
Reproductive performance of pregnant rats fed diets supplemented without (control, CON) or with pectic oligosaccharide (POS) at 800 mg/kg during pregnancy[1].

| Item | CON | POS |
|---|---|---|
| *n* | 8 | 8 |
| Number of rats per litter | | |
| Born | 14.86 ± 0.55 | 17.29 ± 0.75* |
| Born alive | 14.57 ± 0.43 | 17.14 ± 0.74* |
| Birth weights, g | | |
| Average rats born alive per litter | 6.36 ± 0.17 | 5.99 ± 0.24 |
| Rats born alive per litter | 94.14 ± 2.90 | 102.93 ± 4.12 |

*Different from the CON group ($P < 0.05$).
[1] Data are means ± standard errors.

### 3.2. Maternal feed intake and weight gain, number of embryos and fetuses, and uterus index of pregnant rats (Exp. 2 and 3)

On d 7 and 14 of gestation, maternal feed intake, total maternal weight gain and uterus index of rats in CON group were not different from those in POS groups (Fig. 1A, B and D). The number of rat embryos was not affected by POS administration on d 7 of gestation (Fig. 1C), and dietary POS supplementation increased the number of rat fetuses by 12.20% on d 14 of gestation ($P < 0.05$, Fig. 1C).

### 3.3. Microflora and volatile fatty acids in cecal digesta of pregnant rats (Exp. 3)

Supplementing POS in the diet from d 1 to 14 of gestation increased the populations of *Lactobacillus* and *Bifidobacterium* ($P < 0.05$), and decreased the population of *Escherichia coli* ($P < 0.05$), but did not influence the population of total bacteria in the cecal digesta of pregnant rats (Fig. 2A). On d 14 of gestation, in the cecal digesta of pregnant rats, the concentrations of acetic acid, propionic acid and total VFA were enhanced by POS administration ($P < 0.05$), but there was no difference with butyric acid concentration between CON and POS groups (Fig. 2B).

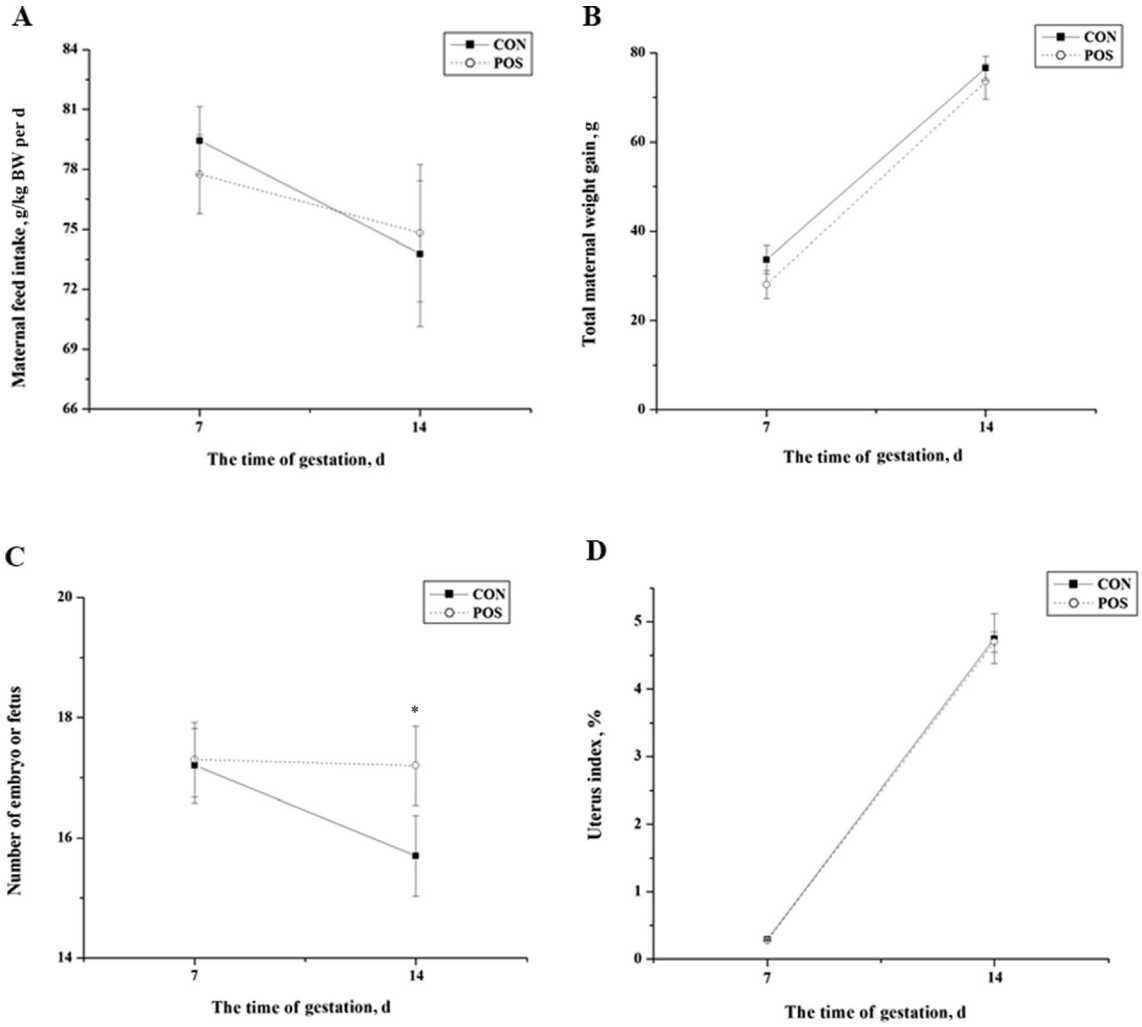


**Fig. 1.** Effect of dietary pectic oligosaccharide (POS) supplementation on maternal feed intake (A) and weight gain (B), number of embryos and fetuses (C), and uterus index (D) of pregnant rats on d 7 and 14 of gestation. *Different from the CON group ($P < 0.05$). Data are means ± standard errors. CON, the control diet; POS, the control diet supplemented with 800 mg/kg of POS.

### 3.4. Serum progesterone, estradiol, nitric oxide and vascular endothelial growth factor concentrations in pregnant rats (Exp. 3)

The effect of dietary POS supplementation on serum progesterone, estradiol, NO and VEGF concentrations in pregnant rats was shown in Fig. 3. On d 14 of gestation, compared with the CON group, serum progesterone and NO concentrations of pregnant rats in the POS group were increased by 25.03% and 6.97%, respectively ($P < 0.05$, Fig. 3A, C), and serum VEGF concentration of pregnant rats in the POS group tended to be enhanced by 5.28% ($P = 0.09$, Fig. 3D). Additionally, POS administration did not affect serum estradiol concentration in pregnant rats (Fig. 3B).

### 3.5. Serum inflammatory cytokine levels in pregnant rats (Exp. 3)

As shown in Fig. 4, on d 14 of gestation, dietary POS supplementation reduced serum IL-2 level by 15.93% ($P < 0.05$), and tended to increase serum IL-10 level by 11.30% ($P = 0.06$), but did not affect serum IL-6 and IFN-γ levels in pregnant rats.

### 3.6. Antioxidant capacity of serum and placenta in pregnant rats (Exp. 3)

Supplementing POS in the diet for pregnant rats from d 1 to 14 of gestation increased T-AOC by 23.18% ($P < 0.05$), tended to enhance T-SOD activity by 10.21% ($P = 0.08$), decreased MDA concentration by 18.43% ($P < 0.05$), and did not affect GSH-Px activity in serum (Table 3). Pectic oligosaccharide administration from d 1 to 14 of gestation tended to increase T-AOC by 18.28% ($P = 0.08$), enhanced T-SOD activity by 17.65% ($P < 0.05$), tended to reduce MDA concentration by 24.79% ($P = 0.06$), and did not affect GSH-Px activity in placenta of pregnant rats (Table 3).

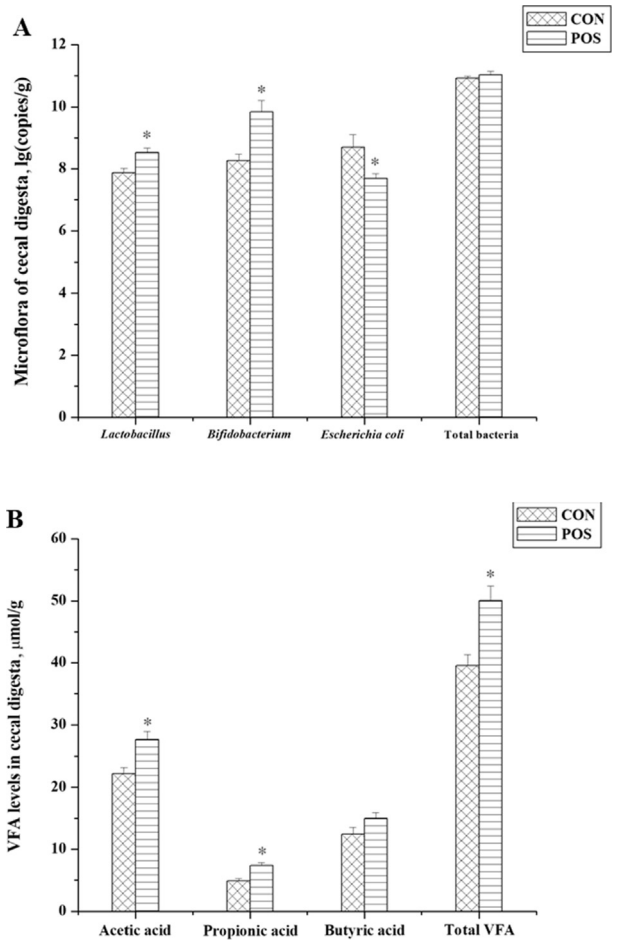


**Fig. 2.** Effect of dietary pectic oligosaccharide (POS) supplementation on microflora (A) and volatile fatty acids (VFA) (B) in the cecal digesta of pregnant rats on 14 d of gestation. * Different from the CON group ($P < 0.05$). Data are means ± standard errors. CON, the control diet; POS, the control diet supplemented with 800 mg/kg of POS.

## 4. Discussion

As a functional oligosaccharide, POS may regulate the physiological function of humans and animals, such as antioxidant capacity, immune function, lipid metabolism, and intestinal microflora (Fanaro et al., 2005; Kang et al., 2009; Li et al., 2010). Our previous studies also showed that POS administration can increase growth performance, antioxidant capacity and gut health of weaned rats, alleviate the effect of rotavirus infection on growth performance, diarrhea, gut dysfunction of weaned piglets via the increase of immunity and gut barrier function, and improve carcass traits, meat quality and lipid metabolism of finishing pigs (Mao et al., 2016a, 2017a, 2017b, 2019a; Chen et al., 2017). In the current study, our novel finding was that dietary POS supplementation could also increase the reproductive performance of pregnant rats.

During the gestation, early pregnancy is the key phase of embryo implantation and survival (Goff, 2002). However, in the phase of middle gestation, fetal resorption derived from all kinds of reasons will also impair the litter size at birth (Jaffe, 2000). In the present study, POS administration did not affect the number of rat embryos on d 7 of gestation, but increased the number of rat fetuses on d 14 of gestation. These demonstrated that the improvement of reproductive performance by dietary POS supplementation of pregnant maternal animals was possibly due to the decrease of fetal resorption in middle gestation.

Pectic oligosaccharide consists of pectic disaccharide and trisaccharide that contain galacturonic acid. These components can not directly be digested and absorbed, and POS is mainly fermented by microflora in the distal intestine (Gómez et al., 2014). Previous studies showed that POS treatment increases the populations of *Lactobacillus* and *Bifidobacterium* in the fermentation substrate (Mandalari et al., 2007; Gullón et al., 2011), and supplementing mixed oligosaccharides (including POS) in diet also enhances the populations of *Lactobacillus* and *Bifidobacterium* in the gut of children (Fanaro et al., 2005). Additionally, our previous studies showed that POS administration increases the populations of *Lactobacillus* and *Bifidobacterium*, and decreases the populations of *E. coli* in the cecal digesta of weaned rats, weaned piglets and finishing pigs (Mao et al., 2016a, 2017a, 2017b, 2019a), which was similar to the microflora results of pregnant rats in this study.

Volatile fatty acids are the main metabolites of gut microflora. In the present study, dietary POS supplementation increased the concentrations of acetic acid, propionic acid and total VFA in the cecal digesta of pregnant rats on d 14 of gestation. This is similar to the results of our recent studies in weaned rats, weaned piglets, and finishing pigs (Mao et al., 2016a, 2017a, 2017b, 2019a). Moreover, following being absorbed, besides being utilized as the energy source of colonic cells and the liver, VFA can also regulate steroid-hormone secretion, antioxidant capacity, and inflammatory cytokine and NO productions (Hamer et al., 2009; Vinolo et al., 2011; Tan et al., 2014; Schönfeld and Wojtczak, 2016; Ye et al., 2019). Thus, we mainly measured and analyzed the relative indices of rats on d 14 of gestation.

In the current study, POS administration enhanced serum progesterone and NO concentrations of pregnant rats on d 14 of gestation. During recognition and maintenance of maternal pregnancy, progesterone and NO play important roles. In addition to

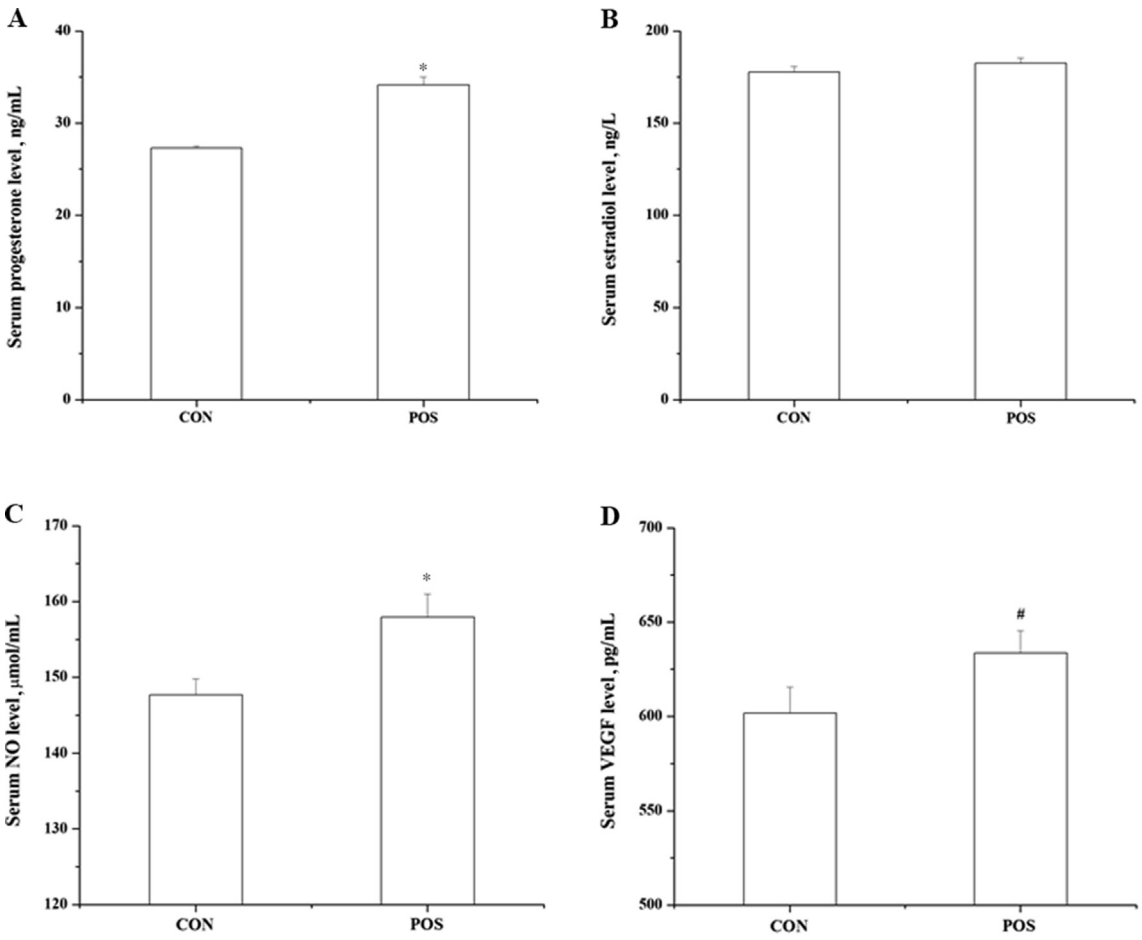


**Fig. 3.** Effect of dietary pectic oligosaccharide (POS) supplementation on serum progesterone (A), estradiol (B), nitric oxide (NO) (C) and vascular endothelial growth factor (VEGF) (D) concentrations in pregnant rats on 14 d of gestation. * Different from the CON group ($P < 0.05$); # Different from the CON group ($P < 0.10$). Data are means ± standard errors. CON, the control diet; POS, the control diet supplemented with 800 mg/kg of POS.

regulating the oviductal and uterine functions, progesterone and NO stimulate angiogenesis via increasing VEGF generation (Rosselli et al., 1998; Spencer, 2002; Cooke, 2003; Kim et al., 2013). We also found that POS treatment increased serum VEGF concentration of pregnant rats on d 14 of gestation. Thus, POS may have the function of enhancing the vascular generation of the fetusl and placenta during the phase of middle gestation.

The redox status is vital for human and animal health. Although humans and animals have the adaptive adjustment of redox status during pregnancy, the production of reactive oxygen species is still enhanced (Fischer and Bavister, 1993; Brison and Leese, 1991). Oxidative stress has been clearly shown in placental tissue, and it impairs placenta function, which will do harm to the development of embryo and fetus (Myatt and Cui, 2004; Agarwal et al., 2005). Our previous studies showed that POS administration can improve the antioxidant capacity in serum, jejunum and ileum of weaned piglets and rats (Mao et al., 2016a, 2017b, 2019a; Chen et al., 2017). In this study, dietary POS supplementation improved the T-AOC and T-SOD activity, and reduced the lipid peroxidation product (namely, MDA) concentration in the serum and placenta of pregnant rats on d 14 of gestation. Thus, POS promoting the maternal antioxidant capacity could be one of the reasons that POS reduced fetal loss during the phase of middle gestation.

In the process of gestation, the maternal cytokine (especially T-helper [Th] cytokine) levels are critical to the pregnancy maintenance (Baines and Gendron, 1990). The increasing Th1 cytokines, such as IL-2 and IFN-γ, prevents the development of embryo and

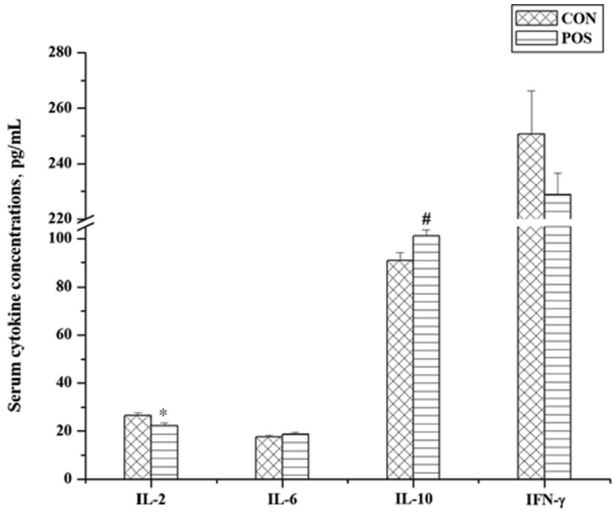


**Fig. 4.** Effect of dietary pectic oligosaccharide (POS) supplementation on serum cytokine levels in pregnant rats on 14 d of gestation. IL-2 = interleukin 2; IL-6 = interleukin 6; IL-10 = interleukin 10; IFN-γ = interferon γ. * Different from the CON group ($P < 0.05$); # Different from the CON group ($P < 0.10$). Data are means ± standard errors. CON, the control diet; POS, the control diet supplemented with 800 mg/kg of POS.

**Table 3**
Antioxidant capacity of serum and placenta in pregnant rats fed diets supplemented without (CON) or with pectic oligosaccharide (POS) at 800 mg/kg from d 1 to 14 of gestation[1].

| Item | CON | POS |
|---|---|---|
| *n* | 7 | 7 |
| Serum | | |
| T-AOC, U/mL | 3.58 ± 0.15 | 4.41 ± 0.28* |
| T-SOD, U/mL | 226.18 ± 8.94 | 249.28 ± 6.48# |
| MDA, nmol/mL | 9.93 ± 0.66 | 8.10 ± 0.30* |
| GSH-Px, U/mL | 635.63 ± 16.93 | 659.57 ± 26.34 |
| Placenta | | |
| T-AOC, U/mg protein | 0.93 ± 0.04 | 1.10 ± 0.06# |
| T-SOD, U/mg protein | 70.82 ± 4.07 | 83.32 ± 2.67* |
| MDA, nmol/mg protein | 1.21 ± 0.08 | 0.91 ± 0.05# |
| GSH-Px, U/mg protein | 158.75 ± 15.00 | 169.30 ± 7.99 |

T-AOC = total antioxidant capacity; T-SOD = total superoxide dismutase; MDA = malondialdehyde; GSH-Px = glutathione peroxidase.
*Different from the CON group ($P < 0.05$).
#Different from the CON group ($P < 0.10$).
[1] Data are means ± standard errors.

fetus, disturbs the process of pregnancy, and induces embryotocia (Tangri and Raghupathy, 1993). The enhancement of Th2 cytokines, including IL-6 and IL-10, inhibits the immunological rejection, promotes the angiogenesis of placenta, and improves the development of embryo and fetus (Chaouat et al., 1990). Our previous study showed that POS administration may regulate the Th cytokine generation, and attenuate the rotavirus-induced inflammation in weaned piglets (Chen et al., 2017). Now, we also found that supplementing POS in diet decreased serum IL-2 level, and tended to increase serum IL-10 concentration of pregnant rats on d 14 of gestation. These results declared that POS improved the Th cytokine production, and then decreased the immunological rejection during the phase of middle gestation.

## 5. Conclusions

In summary, dietary POS supplementation improved the reproductive performance of pregnant rats. This could be not relative with embryo implantation, but be associated with the decrease of fetus loss during the phase of middle gestation. Via further analysis, POS reducing fetus loss was mainly due to the increasing VFA in rat gut, which promoted angiogenesis, increased antioxidant capacity, and reduced immunological rejection. Our novel findings will supply vital implications for decreasing fetus loss and improving pregnant outcome in the non-ruminant mammals.

## Conflicts of interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the content of this paper.

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