Effect of Maternal Folate Deficiency on Growth Performance, Slaughter Performance, and Serum Parameters of Broiler Offspring

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In this study, we aimed to investigate the influence of maternal folate deficiency on the production performance and serum parameters of broiler offspring. The 120 healthy female broilers (30-week-old) were randomly allotted into two groups. The groups were either fed a basal diet supplemented with 2.0 mg/kg folate (NF) or basal diet (FD). The experiment lasted 12 weeks, and 120 fertilized eggs were collected from each group for hatching. In total, 80 chicks were selected from each group and fed under the same conditions. No significant difference was observed in the average daily feed intake, average daily gain, and feed to gain ratio of 21- and 42-day-old broilers between NF and FD groups ($P > 0.05$). Moreover, slaughter performance of 21- and 42-day-old broiler offspring were not affected by the maternal FD. The subcutaneous fat thickness at the age of 21 days increased significantly by maternal FD ($P < 0.01$); however, there was no significant difference between the two groups at 42 days of age ($P > 0.05$). Similarly, no significant differences were detected in the intermuscular fat width, lipid percentage in the liver, breast muscle, and thigh muscle between the NF and FD groups at 21- and 42-days of age ($P > 0.05$). Serum concentrations of MTHFR, DHFR, LEP, IGF2, LPL and HCY in the 21-day-old broilers were not affected by maternal FD ($P > 0.05$), but those of HSL at 21 days of age was enhanced by maternal FD ($P < 0.05$). These findings indicated that maternal folate deficiency had no influence on production performance, slaughter performance, most fat traits of 21- and 42-day-old broiler offspring, and serum parameters of 21-day-old broiler offspring except HSL.

Key words: broiler, folate deficiency, folic acid, performance, serum parameter

Introduction

Folic acid (FA), also named folate, is a water-soluble B vitamin, where one of the vitamin B complexes of FA is equivalent to sphenol glutamic acid. FA is one of several essential vitamins needed for human health and development (Guéant et al., 2013; Deghan Manshadi et al., 2014). In animals, FA is converted into the metabolically active coenzyme, tetrahydrofolic acid (THF), by dihydrofolate reductase. THF participates in several critical reactions as a donor and receptor of the one-carbon unit during the synthesis (or anabolism) of amino acids and nucleic acids (Nazki et al., 2014; Pieroth et al., 2018). A study has shown that dietary restriction of folic acid intake in female rats can increase visceral fat content and lipid metabolism in offspring (Kumar et al., 2013). Folate deficiency (FD) in female mice can lead to short-term memory impairment in the offspring of dams (Jadavji et al., 2015).

Additionally, it was reported that FD during early-mid pregnancy affected piglet body weight, longissimus dorsi muscle fiber number, the content of intramuscular triglyceride, and gene expression. Thus, affecting the overall formation of skeletal muscle in piglets (Li et al., 2013). Conversely, dietary FA supplementation increased egg weight and egg mass and decreased serum glucose levels in young laying hens, and reduced serum uric acid in older laying hens (Jing et al., 2014). Overall, maternal folate levels have a positive impact on the growth and development of their offspring.

To date, studies on the effect of maternal FD on offspring growth and development have mainly focused on mammals. In contrast, the effect of laying hen FD on offspring growth and development has rarely been reported. The present experiment investigated the effects of FD on the production performance, slaughter performance, and serum parameters
of broiler offspring, which will provide a basis for the rational utilization of folic acid in poultry production.

Materials and Methods

Animals, Diets, and Treatments

In total, 120 healthy 30-week-old Arbor Acres (AA) female broilers were randomly allotted into two groups (e.g., the control group and the experimental group). Each group had five replicates for a total of 12 birds.

The control group was fed a basal diet (measured concentration of folate: 0.22 mg/kg) with 2.0 mg/kg folate (normal folate, NF), while the experimental group was fed a basal diet with 0 mg/kg folate (folate deficiency, FD) so that folate only came from corn, soybean meal, and other diets. A standard basal diet containing corn and soybean meal was fed as a mash, and the composition of the basal diet (Table 1) was formulated to meet or exceed the nutritional requirements for female broiler breeders, established by the National Research Council (NRC, 1994). Meanwhile, all male broiler breeders were fed the same standard diet (NRC, 1994) ad libitum. Water, conventional vaccination, and natural ventilation were provided, and hurdles were kept clean and sanitary. The light program was 16 h light and 8 h dark. During the experiment’s final 2 weeks, semen was collected for artificial insemination at 16:00, once every 2 d. The experiment lasted 12 weeks, wherein the final 3 d a total of 120 fertilized eggs were collected in each group for hatching.

Eighty chicks were randomly selected from each group (groups were the same as the above NF and FD). Each of the treatments consisted of five replicate cages with 16 chicks per replicate cage. Corn-soybean meal-based diets (Table 2) were allocated at 1–3 weeks and 4–6 weeks of age, respectively. These chicks of NF and FD groups were fed the same diets (Table 2) and kept under the same environmental conditions and allowed free access to water and mash feed.

The ingredient composition and nutrient level of the basal diet are shown in Tables 1 and 2. All experimental protocols were approved by the Animal and Care Committee of Linyi University.

Sample Collection and Trait Measurement

At 21 and 42 days of age, chicks from each group were weighed after feed deprivation for 12 h with free drinking water, respectively. The residual feed of each group was also weighed. The average daily gain (ADG), average daily feed intake (ADFI), and feed to gain ratio (F/G) were calculated for each group.

Subsequently, two broilers per replicate were randomly selected and sacrificed by jugular vein bleeding. Sera were obtained by gentle centrifugation at 3000 times g and stored at −80°C until use. After collecting blood samples, dressed weight, eviscerated weight, breast muscle weight, thigh muscle weight, liver weight, and abdominal fat weight were recorded to calculate slaughter percentage, whole net carcass percentage, breast muscle percentage, thigh muscle percentage, liver weight percentage, and abdominal fat percentage according to the Terminology of Poultry Production Performance and Statistical Method of Measurement (NY/T823-2004, China). Subcutaneous fat thickness and intermuscular fat width were measured according to the Chicken Quality Grading (NY/T 631-2002, China).

Biochemical Parameter Assays

Serum 5,10-methylenetetrahydrofolate reductase (MTHFR) (Cat. No.: YPG7490), dihydrofolate reductase (DHFR) (Cat. No.: YPG9364), hormone-sensitive lipase (HSL) (Cat. No.: YPG1354), lipoprotein lipase (LPL) (Cat. No.: YPG6714), leptin (LEP) (Cat. No.: YPG1972), insulin-like growth factor 2 (IGF2) (Cat. No.: YPG5206), and homocysteine (HCY) (Cat. No.: YPG2594) were measured using an enzyme-

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**Table 1. Content and nutrition level of diet for broiler breeders**

| Ingredients     | Content (%) | Nutrient levels | Content (%) |
|-----------------|-------------|-----------------|-------------|
| Corn            | 64.5        | ME (MJ kg⁻¹)    | 12          |
| Soybean meal    | 23.50       | CP              | 15.50       |
| Soybean oil     | 2.0         | Ca              | 3.10        |
| Fine limestone  | 7.51        | P, total        | 0.40        |
| CaHPO₄·2H₂O     | 1.80        | Met             | 0.36        |
| Salt            | 0.17        | Lys             | 0.72        |
| Ethoxyquin      | 0.02        | Ile             | 0.56        |
| NaHCO₃          | 0.15        | Arg             | 0.90        |
| Mineral premix¹ | 0.15        | Met + Cys       | 0.62        |
| Vitamin²        | 0.20        | Val             | 0.62        |
| Total           | 100         | Thr             | 0.52        |
|                 |             | Trp             | 0.17        |

¹ The amount of minerals provided per kilogram of diet: Mn 150 mg; Zn 100 mg; Fe 70 mg; Cu 18 mg; I 1.1 mg; Se 0.25 mg.
² The amount of vitamins provided per kilogram of diet: vitamin A 11000 IU, vitamin B₁₂ 12.00 mg, vitamin B₃ 12.00 mg, vitamin B₆ 4.40 mg, vitamin B₁₂ 22.00 μg, vitamin D₃ 3500 IU, vitamin E 100 IU, vitamin K 4.40 mg, niacin 50 mg, pantothenic acid 15.5 mg, biotin 220 μg, choline 1210.0 mg, folic acid 2.0 mg (experiment group: 0 mg).
linked immunosorbent assay (ELISA) kit according to the manufacturer’s protocols (Shanghai Yuping Biotech Co. Ltd., Shanghai, China). Total lipids in the liver, thigh muscle, and breast muscle were extracted using Folch’s method (Folch et al., 1957).

### Statistical Analysis

All statistical analyses were performed with SAS JMP® Pro software, version 13.20. Group data for multiple comparisons were analyzed by ANOVA using the GLM procedure, followed by Duncan’s multiple range test to test for differences. A p-value of less than 0.05 was interpreted as statistically significant. Experimental data were expressed as means±the standard errors of the means (SEM).

### Results

#### Growth Performance

Compared with the NF group (Table 3), the maternal FD group demonstrated a decrease in ADFI and ADG at 21- and 42-day-old broilers, but the difference was not significant (P >0.05). Also, no significant difference was observed in F/G of 21- and 42-day-old broilers between NF and FD groups (P >0.05).

| Trait | 21 Day | 42 Day |
|-------|--------|--------|
|       | NF     | FD     | P-value |
|       | NF     | FD     | P-value |
| ADFI1 (g) | 52.82±1.56 | 51.56±1.58 | 0.652 |
| ADG2 (g) | 42.36±1.23 | 38.77±1.56 | 0.461 |
| F/G3   | 1.25±0.05 | 1.33±0.06 | 0.423 |
|        | 105.26±3.36 | 103.27±3.10 | 0.356 |
|        | 62.02±1.44 | 61.06±2.17 | 0.768 |
|        | 1.70±0.04 | 1.69±0.06 | 0.552 |

1 average daily feed intake; 2 average daily gain; 3 feed to gain ratio

#### Slaughter Performance

Slaughter performance of 21- and 42-day-old broiler offspring, i.e., slaughter percentage, whole net carcass percentage, breast muscle percentage, thigh muscle percentage, liver weight percentage, and abdominal fat percentage, were not affected by maternal FD (P >0.05) (Table 4).

#### Subcutaneous Fat Thickness and Intermuscular Fat Width

As shown in Table 5, the subcutaneous fat thickness at 21-days of age increased significantly by maternal FD (P <0.01). However, there was no significant difference between the two groups at 42-days of age (P >0.05) (Table 5). Similarly, no significant differences were observed in the intermuscular fat width between the NF and FD groups at 21- and 42-days of age (P >0.05) (Table 5).

#### Fat Content Percentage in Liver, Breast Muscle, and Thigh Muscle

As can be seen from Table 6, the lipid percentage in the liver, breast muscle, and thigh muscle of broiler offspring increased as a result of maternal FD. However, there was no significant difference between the two groups (P >0.05).

#### Serum Parameters

To elucidate the effect of maternal FD on serum metabolites, we determined some enzymes that are related to folic acid metabolism.
HSL at 21 days of age was enhanced by maternal FD. Serum concentrations of MTHFR, DHFR, LEP, IGF2, and lipid metabolism using ELISA. The results showed that maternal FD did not significantly affect the growth performance, slaughter performance, or most fat traits of broiler offspring. Only at 21 days of age, the thickness of subcutaneous fat between the NF and FD groups reached a significant difference, which suggests that maternal FD may have had a pronounced influence on the fat deposition in the offspring at an early stage, which then gradually weakened over time. We speculated that maternal FD could be remedied in her offspring by a diet supplemented with folate or synthetic folate, in vivo, during the growth and development of broiler offspring. Future investigations are warranted to explore these critical metabolic pathways.

It was reported that dietary protein restriction of pregnant rats induced persistent, gene-specific epigenetic changes that alter mRNA expression. However, folic acid supplementation prevented these changes (Lillycrop et al., 2005). Similarly, maternal exposure to fluoxetine during gestation and lactation affects DNA methylation of rat offspring’s brains, whereas this effect was eliminated in animals from supplemented with folate acid (Tofoli et al., 2014). Meanwhile, studies in humans and rats have shown that maternal dietary folate restrictions before pregnancy, lead to the occurrence of related diseases in offspring (Kumar et al., 2013; Dominguez-Salas et al., 2014). Recently, Degroote et al. (2018) observed that periconceptional FD led to autism-like traits in Wistar rat offspring (Degroote et al., 2018).

It has been found that mutations in the mouse methionine synthase reductase (MTRR) can lead to abnormal folate metabolism, which causes similar effects as folate deficiency; for example, intrauterine growth restriction, developmental delay, and congenital abnormalities (Padmanabhan et al., 2013; Dominguez-Salas et al., 2014). Future studies in humans and animals are warranted to explore these critical metabolic pathways.

Discussion

Folate is an essential vitamin for the healthy growth and reproduction of animals. Nevertheless, FD will affect the normal physiological functions of animals. For humans, FD or folic acid metabolic deficits can cause several diseases, for example, neural tube malformations, megaloblastic anemia, cleft lip and palate, autism spectrum disorders, and cancer, and so on (Coppen and Bolander-Gouaille, 2005; Stover, 2009; Czeizel et al., 2013; Desai et al., 2016). Currently, research on FD is primarily focused on humans, mice, and rats, with rarely any studies concentrating their investigation on livestock and poultry. The present study is the first research group that studied the effects of maternal FD on the growth and development of broiler offspring. Our results showed that FD did not significantly affect the growth performance, slaughter performance, or most fat traits of broiler offspring. Only at 21 days of age, the thickness of subcutaneous fat between the NF and FD groups reached a significant difference, which suggests that maternal FD may have

Table 4. Effects of maternal FD on slaughter performance of broiler offspring (% (n = 10)

| Trait                        | 21 Day (%) | 42 Day (%) |
|------------------------------|------------|------------|
|                              | NF          | FD         | P-value | NF          | FD         | P-value |
| Slaughter percentage         | 91.16±8.12  | 89.57±9.32 | 0.356   | 91.22±11.21| 90.79±9.36 | 0.455   |
| Whole net carcass percentage | 65.09±3.56  | 64.73±4.55 | 0.163   | 80.18±10.28| 80.53±9.57 | 0.730   |
| Breast muscle percentage     | 27.05±4.22  | 26.32±3.32 | 0.431   | 26.71±2.56 | 26.45±1.52 | 0.915   |
| Thigh muscle percentage      | 21.93±3.22  | 20.86±2.31 | 0.123   | 20.54±2.25 | 20.81±3.26 | 0.934   |
| Liver weight percentage      | 3.71±0.05   | 4.03±0.03  | 0.812   | 2.59±0.02  | 2.47±0.03  | 0.317   |
| Abdominal fat percentage     | 2.04±0.01   | 2.74±0.02  | 0.226   | 2.45±0.03  | 2.35±0.02  | 0.614   |

Table 5. Effects of maternal FD on subcutaneous fat thickness and intermuscular fat width of broiler offspring (n = 10)

| Trait                  | 21 Day (mm) | 42 Day (mm) |
|------------------------|-------------|-------------|
| Subcutaneous fat thickness | 4.75±0.20   | 5.82±0.20** | 0.003 |
| Intermuscular fat width | 7.75±0.38   | 8.18±0.25   | 0.373 |

**P<0.01

Table 6. Effects of maternal FD on lipid percentage in liver, breast muscle and thigh muscle of broiler offspring (n = 10)

| Trait     | 21 Day (%) | 42 Day (%) |
|-----------|------------|------------|
|           | NF          | FD         | P-value | NF          | FD         | P-value |
| Liver     | 3.00±0.29   | 3.12±0.11  | 0.943   | 4.62±0.66   | 4.90±0.78  | 0.788   |
| Breast muscle | 1.93±0.48  | 3.46±1.75  | 0.443   | 1.26±0.23   | 1.92±0.25  | 0.068   |
| Thigh muscle | 7.10±1.12  | 9.74±0.84  | 0.088   | 7.76±1.42   | 7.97±1.42  | 0.995   |
et al., 2013). Mutations in MTRR can also cause epigenetic instability and transgenerational effects on development (Padmanabhan et al., 2013). Similar findings have been observed in MTHFR. An MTHFR deficiency or a reduced intake of folate in pregnant mice increased levels of plasma HCY in offspring (Jadavji et al., 2015). Our previous research also showed that serum HCY level were elevated in 42-day-old broilers by maternal FD (Xing et al., 2018), which was in agreement with results from Jadavji et al. (2015). In contrast, plasma HCY concentrations were significantly reduced for the Hyline W98 hens consuming the highest levels of FA (Hebert et al., 2005).

In ewes, restricting the supply of folate, vitamin B12, and/or methionine before pregnancy leads to heavier and fatter adult offspring (Sinclair et al., 2007). Our previous study indicated that the folate-deficient food of broiler breeders remarkably increased the size of the lipid droplets in offspring (Xing et al., 2018). However, experimental results in this study did not reveal an increase in the abdominal fat of broiler offspring, which may be related to animal species, age, and feeding patterns. If FD occurs during early-mid pregnancy in sows, there is no significant difference in body length and body height (Li et al., 2013). This is partly consistent with our results.

At present, folate supplementation in diets has been studied more aggressively in poultry. It was reported that FA supplementation in diets could significantly increase egg yolk folate deposition. However, the response of egg folate to dietary folic acid supplementation was saturable, with 90% of maximal egg folate levels established at approximately 4 mg/kg folic acid diets (House et al., 2002). Hence, the folate deposition in eggs could not be elevated by increasing dietary folate supplementation in chickens (House et al., 2002; Hebert et al., 2005; Hoey et al., 2009). Studies in chickens have shown that levels of total protein, globulin, and albumin in plasma or serum were enhanced by dietary FA supplementation (Gursu et al., 2004; El-Demerdash et al., 2006).

Similarly, for young laying hens, FA increased biochemical constituents, enhanced generation of total IgG, and caused pleiotropic effects in inflammatory responses (Munyaka et al., 2012). In the present study, most serum parameters of 21-day-old broilers did not change significantly. However, the same serum parameters of 42-day-old broiler offspring were increased by maternal FD from our previous study (Xing et al., 2018), speculating these changes may be related to age, because previous research has shown that the young and older laying hens responded differently to dietary FA (Jing et al., 2014). Recently, a study has demonstrated that paternal folate supplementation is beneficial to the growth and organ development of broiler offspring, and paternal folate could transgenerationally regulate lipid and glucose metabolism in broiler offspring (Wu et al., 2019).

In conclusion, maternal folate deficiency had no significant effects on growth performance, slaughter performance, most fat traits of 21- and 42-day-old broiler offspring, or serum parameters of 21-day-old broiler offspring except
Folic acid metabolism is an extremely complex process in animals. The effects of maternal folate deficiency on offspring are different for different animals, and additional research is required to clarify the folate metabolic mechanism.

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Conflict of Interest

The authors declare no conflict of interest.

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