# Correlations of Serum Progesterone Concentration with Uterine and Fetal Weights at Weeks 7 and 15 of Pregnancy in Javanese Thin-Tail Ewes

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**ABSTRACT :** Seventeen pregnant ewes (8 superovulated and 9 non-superovulated) were used to study correlations of maternal serum progesterone concentrations with uterine and fatal weights at weeks 7 and 15 of pregnancy. Statistical analyses indicated that uterine growth during the first 7 weeks of pregnancy highly associated with maternal serum progesterone concentration (r=0.87 and 0.85, with wet and dry uterine weights, respectively). Ewes with higher maternal serum progesterone concentrations had higher total and average fetal weights at week 7 of pregnancy (r=0.89 and 0.86, respectively). At week 7 of pregnancy, wet and dry uterine weights highly correlated ($p<0.01$) with total and average fatal weights (r=0.99 and 0.80, 0.98 and 0.75, respectively). Maternal serum progesterone concentrations, however, did not correlate ($p>0.05$) with wet and dry uterine weights (r=0.36 and 0.47, respectively) and with total and average fetal weights (r=0.20 and 0.58, respectively) at week 15 of pregnancy. However, wet and dry uterine weights had high correlation with total fetal weight (r=0.97 and 0.95, respectively), without significant correlation with average fetal weight. It was concluded that during the embryonic stage of pregnancy, the levels of maternal progesterone were highly correlated with uterine and fetal growths, while during the fetal stage pregnancy, the correlation became less evident. *(Asian-Aus. J. Anim. Sci. 1999. Vol. 12, No. 6 : 854-861)*

**Key Words :** Superovulation, Progesterone, Uterine Weight, Fetal Weight, Pregnancy, Sheep

## INTRODUCTION

Birth weight and postnatal life of many domestic animals are profoundly affected by prenatal growth and conditions (Dziuk, 1992). Growth and development of the embryo during the embryonic stage of pregnancy are influenced by uterine growth and development (Denker, 1994), embryo-maternal interactions before implantation (Gandolfi et al., 1992) and nutrients and growth factors exchanges between the embryo and the uterus (Ashworth, 1992).

Growth and development of the uterine tissues with the overall biochemical changes before implantation are initiated by estradiol secreted during preovulation, which are then continued by progesterone (Mulholland et al., 1994) and probably by other hormones and growth factors secreted by the corpus luteum during the luteal phase of the estrous eyete. Growth and development of the fetus during the fetal stage of pregnancy are affected by placental growth and development (Robinson et al., 1995), nutrients availabilities in the maternal, placental and the fetal circulations (Harding and Johnston, 1995; Hay, Jr., 1995), and the endocrine status of the mother and the fetus (Fowden, 1995).

The endocrine status of pregnant animals prior to implantation, which to the no the most part is dictated by the corpus luteum and is represented by progesterone, plays a key role in initiating a cascade of uterine growth and secretions (Knight et al., 1977; Mulholland et al., 1994). Ewes with higher mean serum progesterone during pregnancy give birth to heavier lambs at parturition (Manalu and Sumaryadi, 1998b). The effects of superovulation on maternal serum progesterone concentration, uterine and fetal weigh at weeks 7 and 15 of pregnancy from the same experiment are reported (Manalu et al., 1998). Superovulation prior to mating in sheep dramatically increases maternal serum progesterone concentration (by 354 and 84% during weeks 7 and 15 of pregnancy, respectively) which associated with the increase in uterine weight by 66 and 37%, and individual fatal weight by 40 and 24%, respectively.

The objective of this present paper was to correlate mean maternal serum progesterone concentration with uterine and fetal weights at weeks 7 and 15 of pregnancy.

## MATERIALS AND METHODS

### Experimental design and protocol

Forty of Javanese thin-tail ewelambs, with similar weight (14 to 16 kg) and age (1 to 1.5 years) at the beginning of experiment, were maintained in an individual pen with a two-month adaptation to the experimental conditions prior to treatment.

The experimental ewes were injected twice with 7.5 mg $PGF_{2\alpha}$ (i.m) at an 11-day interval. Twenty of the experimental ewes were injected with 700 IU PMSG (Folligon, Intervet, North Holland) at the same time of the last prostaglandin injection (around the end

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of diestrus), to stimulate superovulation and to increase circulating maternal progesterone concentrations, and the others (20 ewes) with saline as a control. Two days after the last prostaglandin injections, on the onset of estrous cycle, the experimental ewes were mated individually. At the beginning of the experiment, 20 ewes were assigned to be sacrificed at week 7 of pregnancy, and the others (20 ewes) at week 15 of pregnancy. Of 20 ewes slaughtered at week 7 of pregnancy, only nine ewes [6 non-superovulated (with CL number 3.0±0) and 3 superovulated (with CL number 7.0±0.6) ewes] were actually pregnant. Of 20 ewes slaughtered at week 15 of pregnancy, only eight ewes [3 non-superovulated (with CL number 2.7±0.7) and 5 superovulated (with CL number 8.2±1.1) ewes] were actually pregnant (tables 1 and 3). The others were nonpregnant and aborted prior to slaughtering at the predetermined age of pregnancy, and were excluded from data analysis. Pregnancy was determined by the presence of fetus at slaughtering in respective age of pregnancy. Number and weight of fetuses were determined, and the uterus (including placentome) was excised to determine its wet weight. Then the uterus was dried at 105℃ to obtain dry weight.

**Blood sampling and processing**

Blood samples (10 ml) were drawn with plain vacutainer or sterile syringes from the jugular vein (0900 to 1000 h) on days 2 and 3 after the last prostaglandin injection and at weeks 2, 4, 7, 10, and 15 of pregnancy. The weeks of blood sampling were determined with prior knowledge that maternal serum progesterone in Javanese thin-tail ewes did not change significantly from week one to week seven of pregnancy, and increased linearly from week eight to week 17 of pregnancy (Manalu and Sumaryadi, 1998a). The blood samples were allowed to clot in a cool ice box and transported to the laboratory for further separation of serum by centrifugation. The serum samples were then kept frozen for further progesterone analyses.

**Progesterone analyses**

Concentrations of serum progesterone were measured in duplicated by the solid-phase technique radio-immunoassay (Diagnostic Products Corporation, Los Angeles, CA) using $I^{125}$ progesterone as a tracer, with slight modification for ovine progesterone concentration ranges (Manalu and Sumaryadi, 1998a). The progesterone assay used the whole serum without prior ether extraction. The radioactivity of $I^{125}$-progesterone-bound tubes was counted with an automatic gamma counter. The concentrations of standard progesterone used to construct a standard curve ranged from 0.1 to 20 ng/ml. A sample volume of 100 $\mu\ell$ serum was used in the assay for samples with progesterone concentrations ranged from 0.1 to 20 ng/ml. For samples with progesterone concentrations lower than 0.1 ng/ml, sample volume was increased to 200 $\mu\ell$ to bring the progesterone concentrations to the range of concentration used in the standard curve. All sample's progesterone concentrations were within the range of concentrations of standard progesterone used to construct the standard curve. Inter- and intra-assay variations coefficients were 7.5 and 2.0%, respectively. The concentrations of progesterone were parallel in the sample volumes of 50, 100 and 200 $\mu\ell$.

**Statistical analyses**

Correlations of average of maternal serum progesterone concentration during the respective age of pregnancy with wet and dry weights of the uterus, total and average fetal weights, and correlations of wet and dry weights of the uterus with total and average fetal weights in respective age of pregnancy were calculated using simple linear regression analyses (Neter et at., 1985).

## RESULTS

**Week 7 of pregnancy**

The number of corpora lutea and fetuses in the non-superovulated and superovulated ewes slaughtered at week 7 of pregnancy are presented in table 1. In this group of ewes, superovulated had higher number of corpora lutea and fetuses than non-superovulated ewes. Maternal serum progesterone concentrations during the first 7 weeks of pregnancy ranged from 3.2 to 24.9 ng/ml, being lower in the non-superovulated and higher in the superovulated ewes (with means 4.6 ±0.4 and 20.8±1.9 ng/ml, respectively) (table 1). At weeks 2 to 7 of pregnancy, superovulated ewes had a significantly higher progesterone concentrations (table 2). Wet uterine weight ranged from 60.1 to 301.0 g, and similar to progesterone profiles, being lower in the non-superovulated and higher in the superovulated ewes (with means 83.3±5.5 and 254.8±19.5 g, respectively). When expressed in dry uterine weight, the range was from 6.1 to 33.6 g (with means 9.9± 0.8 and 28.6±2.6 g, in the non-superovulated and superovulated ewes, respectively). Total fatal weight ranged from 8.5 to 40.6 g, again being lower in the non-superovulated and higher in the superovulated ewes (with means 9.5±0.3 and 34.5±2.6 g, respectively). Average fetal weight ranged from 8.5 to 13.5 g with superovulated ewes had consistently higher average fetal weight than non-superovulated ewes (with means 9.5±0.3 and 13.2±1.0 g, in the non-superovulated and superovulated ewes, respectively) (table 1).

Correlation analyses indicated that higher mean

**Table 1.** Number of corpora lutea, fetuses, fetal and uterine weight and mean serum progesterone of the non-superovulated and superovulated ewes slaughtered at week 7 of pregnancy

| Treatment | Animal ID | Number of | | Fetal weight (g) | | Uterine weight (g) | | Mean Progesterone (Weeks 2-7) |
|---|---|---|---|---|---|---|---|---|
| | | CL | Fetus | Total | Individual | Wet | Dry | (ng/ml) |
| Non-superovulation | 1 (80) | 3 | 1 | 8.50 | 8.50 | 96.10 | 10.98 | 3.1962 |
| | 2 (79) | 3 | 1 | 9.60 | 9.60 | 99.50 | 12.05 | 3.9927 |
| | 3 (86) | 3 | 1 | 10.60 | 10.60 | 81.90 | 10.52 | 4.2947 |
| | 4 (19) | 3 | 1 | 8.50 | 8.50 | 60.10 | 6.11 | 4.3308 |
| | 5 (10) | 3 | 1 | 10.00 | 10.00 | 89.10 | 9.97 | 5.8086 |
| | 6 (06) | 3 | 1 | 9.50 | 9.50 | 73.10 | 9.98 | 5.8860 |
| | Mean | 3 | 1 | 9.45 | 9.45 | 83.30 | 9.94 | 4.5848 |
| | SE | 0 | 0 | 0.31 | 0.31 | 5.54 | 0.76 | 0.4328 |
| Superovulation | 7 (35) | 7 | 3 | 40.60 | 13.53 | 301.00 | 33.56 | 16.7923 |
| | 8 (34) | 6 | 3 | 32.90 | 10.97 | 242.30 | 29.55 | 20.7083 |
| | 9 (38) | 8 | 3 | 30.00 | 15.00 | 221.00 | 22.75 | 24.8820 |
| | Mean | 7.0 | 3 | 34.50 | 13.17 | 254.77 | 28.26 | 20.7942 |
| | SE | 0.6 | 0 | 2.58 | 0.96 | 19.53 | 2.58 | 2.3356 |

**Table 2.** Serum progesterone concentrations of non-superovulated and superovulated ewes 2 and 3 days after the last prostaglandin injection and at weeks 2, 4, and 7 of pregnancy in the ewes slaughtered at week 7 of pregnancy

| Treatment | Animal ID | Progesterone concentration (ng/ml) | | | | | |
|---|---|---|---|---|---|---|---|
| | | day-2 | day-3 | week-2 | week-4 | week-7 | Mean Weeks 2-7 |
| Non-superovulation | 1 (80) | 0.1058 | 0.0661 | 2.4068 | 2.2753 | 4.9064 | 3.1962 |
| | 2 (79) | 0.0827 | 0.0543 | 2.9092 | 3.6937 | 5.3752 | 3.9927 |
| | 3 (86) | 0.1881 | 0.0599 | 5.6290 | 4.5919 | 2.6632 | 4.2947 |
| | 4 (19) | 0.2355 | 0.0959 | 3.6167 | 4.0752 | 5.3004 | 4.3308 |
| | 5 (10) | 0.1431 | 0.0595 | 3.7197 | 5.1020 | 8.6040 | 5.8086 |
| | 6 (06) | 0.2949 | 0.1209 | 4.9606 | 5.6290 | 7.0684 | 5.8860 |
| | Mean | 0.1750 | 0.0761 | 3.8737 | 4.2279 | 5.6529 | 4.5848 |
| | SE | 0.0329 | 0.0108 | 0.4978 | 0.4824 | 0.8248 | 0.4328 |
| Superovulation | 7 (35) | 0.5706 | 0.1949 | 10.7395 | 9.3982 | 30.2392 | 16.7923 |
| | 8 (34) | 0.1635 | 0.1353 | 14.2221 | 15.6912 | 32.2116 | 20.7083 |
| | 9 (38) | 0.1461 | 0.1184 | 16.7148 | 11.8488 | 46.0824 | 24.8820 |
| | Mean | 0.2934 | 0.1495 | 13.8921 | 12.3127 | 36.1777 | 20.7942 |
| | SE | 0.1387 | 0.0232 | 1.7328 | 1.8314 | 4.9850 | 2.3356 |

maternal serum progesterone concentrations during the first 7 weeks of pregnancy associated with higher ($p<0.01$) wet and dry uterine weights at week 7 of pregnancy ($r=0.87$ and 0.85, respectively) (figure 1). Ewes with higher mean maternal serum progesterone concentrations during the first 7 weeks of pregnancy had significantly higher ($p<0.01$) total and average fetal weights ($r=0.89$ and 0.86, respectively) (figure 1). Wet uterine weight highly correlated ($p<0.01$) with total and average fetal weights ($r=0.99$ and 0.80, respectively) (figure 2). Dry uterine weight significantly correlated ($p<0.01$) with total and average fetal weights ($r=0.98$ and 0.75, respectively) (figure 2).

**Week 15 of pregnancy**

The number of corpora lutea and fetuses in the non-superovulated and superovulated ewes slaughtered at week 15 of pregnancy are presented in table 3. In this group of ewes, superovulated had higher number of corpora lutea than non-superovulated ewes without significant difference in fetal number. Mean maternal serum progesterone concentration during 15 weeks of pregnancy ranged from 4.4 to 20.9 ng/ml, being lower in the non-superovulated and higher in the superovulated ewes (with means $6.9\pm1.4$ and $12.8\pm2.0$ ng/ml, respectively) (table 3). At weeks 2 to 15 of pregnancy, superovulated ewes had a significantly

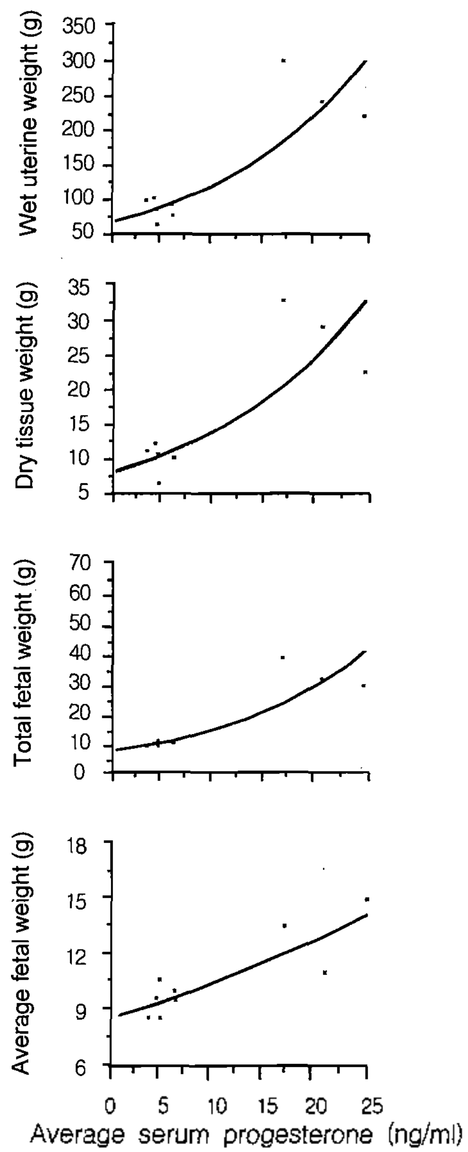


**Figure 1.** Wet and dry uterine weights, total and average fetal weights at week 7 of pregnancy at various serum progesterone concentrations during the first 7 weeks of pregnancy in Javanese thin-tail ewes

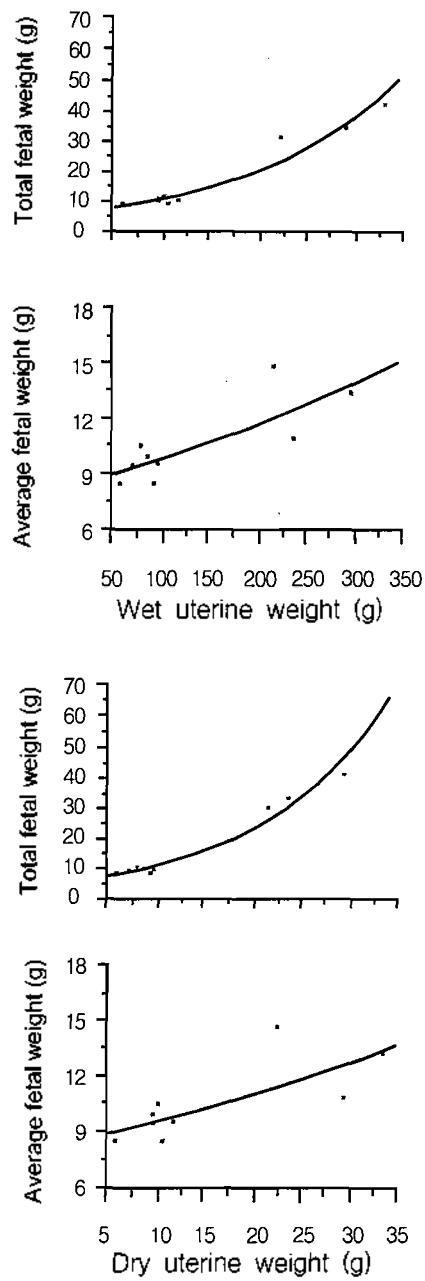


**Figure 2.** Total and average fetal weights at various wet and dry uterine weights at week 7 of pregnancy in Javanese thin-tail ewes

higher progesterone concentrations (table 4). Wet uterine weight ranged from 332.8 to 1080.0 g, being lower in the non-superovulated aud higher in the superovulated ewes (with means 482.8±64.3 and 663.1 ±96.0 g, respectively). When expressed in dry uterine weight, the range was from 36.4 to 105.9 g (with means 50.6±6.0 and 67.7±9.1 g, in the non-superovulated and superovulated ewes, respectively). Total fetal weight ranged fiom 497.6 to 2078.0 g, being lower in the non-superovulated ewes and higher in the superovulated ewes (with means 885.2±169.3 and 1137.8±230.0 g, respectively). Average fetal weight ranged from 435.0 to 775.1 g, being lower in the non-superovulated and higher in the superovulated ewes (with means 525.5±32.1 and 652.0±64.9 g, respectively) (table 3).

Mean maternal serum progesterone concentration during the first 15 weeks of pregnancy, however, did not significantly correlate ($p>0.05$) with wet and dry uterine weights ($r=0.36$ and 0.47, respectively) and with total and average fetal weights ($r=0.20$ and 0.58, respectively) (figure 3). However, wet and dry uterine weights had high correlation with the total fetal weight ($r=0.97$ and 0.95, respectively), without significant correlation with the average fetal weight (figure 4).

**Table 3.** Number of corpora lutea, fetuses, fetal and uterine weight and mean serum progesterone of the non-superovulated and superovulated ewes slaughtered at week 15 of pregnancy

| Treatment | Animal ID | Number of | | Fetal weight (g) | | Uterine weight (g) | | Mean Progesterone (Weeks 2-15) (ng/ml) |
|---|---|---|---|---|---|---|---|---|
| | | CL | Fetus | Total | Individual | Wet | Dry | |
| Non-superovulation | 1 (89) | 2 | 1 | 497.60 | 497.60 | 332.80 | 36.38 | 4.3815 |
| | 2 (90) | 4 | 2 | 951.60 | 475.80 | 523.10 | 54.54 | 6.1433 |
| | 3 (97) | 2 | 2 | 1206.40 | 603.20 | 592.60 | 60.96 | 10.2309 |
| | Mean | 2.67 | 1.67 | 885.20 | 525.53 | 482.83 | 50.63 | 6.9186 |
| | SE | 0.67 | 0.33 | 207.29 | 39.34 | 77.65 | 7.36 | 1.7325 |
| | 4 (68) | 12 | 1 | 770.00 | 770.00 | 534.70 | 50.61 | 8.4343 |
| Superovulation | 5 (73) | 7 | 3 | 1305.10 | 435.03 | 650.00 | 66.81 | 8.5801 |
| | 6 (50) | 7 | 1 | 760.00 | 760.00 | 492.70 | 50.04 | 12.3350 |
| | 7 (03) | 6 | 4 | 2078.78 | 519.70 | 1080.00 | 105.87 | 13.4597 |
| | 8 | 9 | 1 | 775.10 | 775.10 | 558.10 | 65.13 | 20.9362 |
| | Mean | 8.2 | 2.0 | 1137.80 | 651.97 | 663.10 | 67.69 | 12.7491 |
| | SE | 1.07 | 0.63 | 257.20 | 72.57 | 107.36 | 10.17 | 2.2771 |

**Table 4.** Serum pogesterone concentrations of non-superovulated and superovulated ewes 2 and 3 days after the last prostaglandin injection and at weeks 2, 4, 7, 10 and 15 of pregnancy in the ewes slaughtered at week 15 of pregnancy

| Treatment | Animal ID | Progesterone concentration (ng/ml) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Day-2 | Day-3 | Week-2 | Week-4 | Week-7 | Week-10 | Week-15 | Mean Weeks 2-15 |
| Non-superovulation | 1 (89) | 0.1546 | 0.1021 | 3.4919 | 3.9903 | 3.9744 | 4.4784 | 5.9724 | 4.3815 |
| | 2 (90) | 0.1279 | 0.0689 | 2.6930 | 2.5281 | 3.5520 | 7.1684 | 14.7748 | 6.1433 |
| | 3 (97) | 0.0875 | 0.0782 | 5.6290 | 3.4675 | 14.0660 | 9.1012 | 18.8908 | 10.2309 |
| | Mean | 0.1233 | 0.0831 | 3.9380 | 3.3286 | 7.1975 | 6.9160 | 13.2127 | 6.9186 |
| | SE | 0.0195 | 0.010 | 0.8764 | 0.4278 | 3.4364 | 1.3404 | 3.8101 | 1.7325 |
| | 4 (68) | 0.1962 | 0.1217 | 5.7086 | 4.4647 | 5.8476 | 15.3028 | 10.8480 | 8.4343 |
| Superovulation | 5 (73) | 0.1705 | 0.0875 | 4.4025 | 5.2473 | 5.3376 | 12.9296 | 14.9836 | 8.5801 |
| | 6 (50) | 0.3466 | 0.1804 | 9.0104 | 8.2244 | 9.0376 | 14.2652 | 21.1372 | 12.3350 |
| | 7 (03) | 0.1717 | 0.1184 | 5.2106 | 5.5505 | 6.0144 | 18.7588 | 31.7642 | 13.4597 |
| | 8 (45) | 2.6001 | 0.1431 | 16.0252 | 13.7314 | 30.0276 | 19.7036 | 25.1932 | 20.9362 |
| | Mean | 0.6970 | 0.1302 | 8.0714 | 7.4437 | 11.2530 | 16.1920 | 20.7852 | 12.7491 |
| | SE | 0.4769 | 0.0154 | 2.1374 | 1.6945 | 4.7384 | 1.3052 | 3.6912 | 2.2771 |

## DISCUSSION

The results of the present study strongly confirmed that the increased endogenous secretion of progesterone by superovulation prior to mating highly associated with the higher uterine and fetal growth and development as measured at week 7 of pregnancy. The highly significant correlation of maternal serum progesterone concentration with uterine weight at week 7 of pregnancy indicated a greater hormonal stimulation to the uterus growth and development. The increased serum progesterone concentrations could have a dramatic effect on the stimulation of uterine growth, since progesterone is found to direct gene expression in uterine stromal cells (Mulholland et al., 1994). Some other hormones and growth factors secreted by the corpora lutea (i.e. estradiol, relaxin and growth factors) might have been increased and have additive effects on uterine growth.

Greater uterine growth could increase uterine secretions (Mulholland et al., 1994). The increased uterine growth could have improved the uterine secretion and the synchrony between uterus and embryo and fetus (Ashworth, 1992; Gandolfi et al., 1992; Geisert et al., 1992) leading to a greater fetal growth. Better developed uterine environment could increase nutrients and growth factor secretions and exchanges required to support the developing embryo (Findlay et al., 1981; Bell, 1984; Ashworth and Bazer, 1989a, b; Ashworth et al., 1989; Ashworth, 1992).

The results of this experiment suggested that the positive correlation of progesterone with uterine and

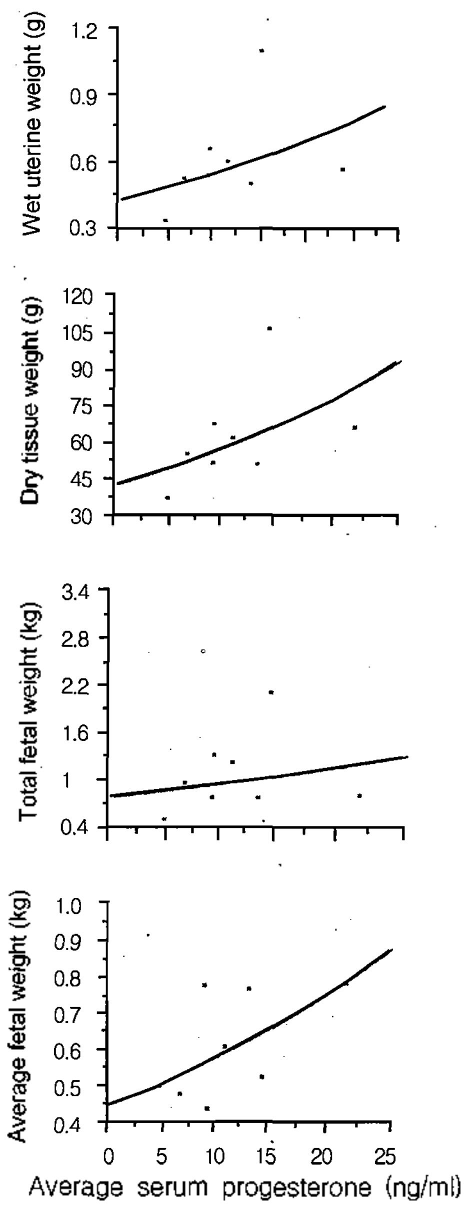


**Figure 3.** Wet and dry uterine weights, total and average fetal weights at week 15 of pregnancy at various average serum progesterone concentrations during the first 15 weeks of pregnancy in Javanese thin-tail ewes

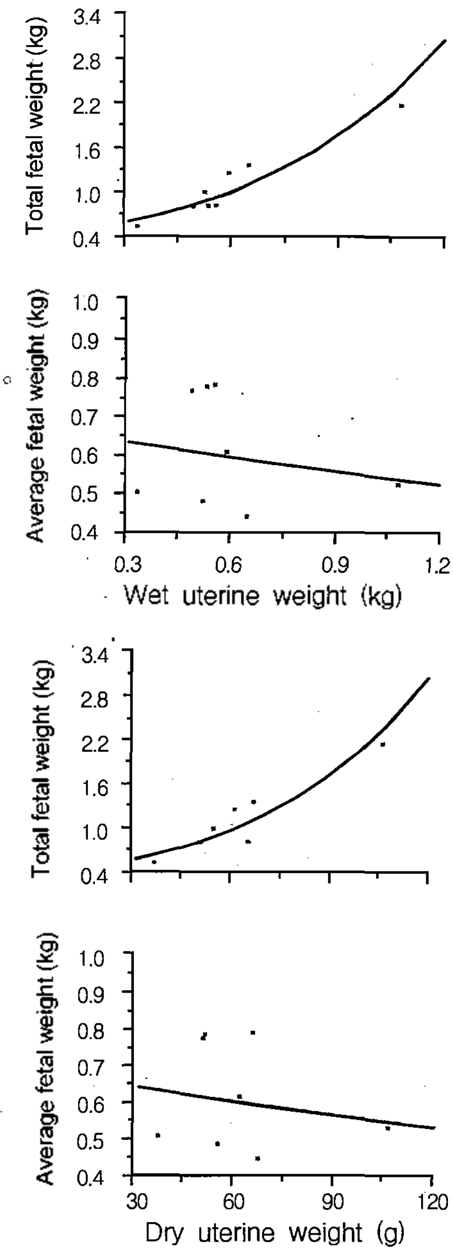


**Figure 4.** Total and average fetal weights at various wet and dry uterine weights at week 15 of pregnancy in Javanese thin-tail ewes

fetal growth was more evident in the first 7 weeks than 15 weeks of pregnancy. During the fetal stage of pregnancy, maternal serum progesterone concentrations did not correlate well with the uterine growth and fetal development. However, uterine weight had high correlation with total fatal weight but tended to be negatively correlated with average fetal weight. These data suggested that uterine weight during the fetal stage of pregnancy is more associated with total fetal weight or litter size than maternal progesterone concentration, as is also reported by Rattray et al. (1974). Average fetal weight or individual fetal weight at the fetal stage of pregnancy in this study was not much correlated with the levels of maternal progesterone and the degree of uterine growth. This probably due to the fact that the uterus does not actively synthesize and secrete nutrients and growth factor required by the developing fetus. At this stage of pregnancy, the fetus extracts its nutrient from the maternal circulation through the placenta. Therefore, the degree of uterine and placental growth does not directly influence the supply of nutrients required by the fetus. However, other reports (Knight et al., 1977; Wu et al., 1987; Wu et al., 1989; Robinson et al., 1995) indicate that uterine length and space to certain limit significantly affect fetal growth, and ewes with, higher progesterone concentration during pregnancy give birth to heavier lambs at parturition (Manalu and Sumaryadi, 1998b).

The effect of progesterone concentration during the fetal stage of pregnancy on fetal development could be, in part, mediated by the reported effects of progesterone on body energy reserves partitioning to the placenta. Some reports indicate that higher progesterone levels could mobilize more fatty acid and glucose from body reserves to the maternal circulation (Shirling et al., 1981; Sutter-Dub et al., 1981; Fowden, 1995) that in turn could be used by the fetus through the placenta to increase fetal growth (Robinson et al., 1995; Fowden, 1995). A better developed placenta produces more placental lactogen and other hormones and factors (Robinson et al., 1995) that could eventually influence fetal growth through their effects on maternal body energy reserves mobilization (Annison et al., 1984; Bell, 1984; Fowden, 1995) and fetal glycogen synthesis (Hill, 1989; Breier et al., 1994). However, the effects of progesterone and other hormones in fetal growth during the fetal stage of pregnancy probably were more evident during late pregnancy i.e. the fastest growth of the fetus. At the age of pregnancy observed in this experiment, the nutrients supply probably was not a limiting factor, so the reported effect of progesterone on fetal growth was not evident.

## CONCLUSION

Fetal weight at week 7 of pregnancy was closely associated with maternal serum progesterone concentration and uterine weight. Uterine weight at week 7 of pregnancy highly correlated with maternal serum progesterone concentration. During the fetal stage of pregnancy, uterine and fetal weights were not closely associated with maternal serum progesterone concentration. Uterine weight correlated well with the total weight or litter size without significant relationship with individual fetal weight.

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