NUTRITION AND PLACENTAL DEVELOPMENT

R. W. KELLY

Summary

Placental weight is highly correlated (generally r > 0.6) with birthweight and therefore survival and growth rate of the newborn mammal. In sheep the growth and development of the placenta precedes the period of rapid fetal growth, while in humans the relationship between the two is closer. Placental growth can be followed in sheep using measurement of cotyledon diameter. Studies are reported showing that maternal undernutrition during days 30 to about 100 of pregnancy can affect placental growth and development, but that at other times during pregnancy the placenta is not sensitive to maternal undernutrition. While the majority of evidence indicates that undernutrition in mid pregnancy will decrease placental size, there is limited data to support the contention that if ewes start the experimental period in high liveweight or condition, the underfed ewes will have heavier placentas.

I. INTRODUCTION

Placenta means flat cake in Greek, a description appropriate to the shape of the human placenta. The focus of considerable research on the placenta has been driven because of its important relationship with fetal growth and therefore birthweight in mammals (e.g. humans - see review by Hytten and Leitch 1971, sheep - Mellor 1983). This review will concentrate on the effect of nutrition on the development of the placenta in ewes, with some limited reference to women.

The correlation coefficients between placental weight and birthweight in both ewes and women ranges between 0.5 - 0.9, indicating that a substantial proportion of the variation in birthweight can be associated with variations in placental weight. Birthweight is important principally because it is associated with the survival and early growth of the newborn. There are direct relationships between size of the newborn and its vigour and energy reserves, as well as indirect links with the condition of the mother and milk production, and therefore her mothering ability, infant survival and growth. The effect of birthweight is of greater importance in multiple than single births, since multiples are on average of lower birthweight, have greater surface area:weight ratio resulting in more rapid heat loss, less energy reserves and in total greater energy demand from the mother in lactation, than single born young. There is some evidence that low birthweight is also associated with lifelong consequences, such as poorer wool quality in sheep and increased blood pressure and coronary heart diseases in humans (Barker 1990).

Division of Animal Industries, W A Department of Agriculture, South Perth WA 6151

II. THE IMPORTANCE OF PLACENTAL SIZE

In simplistic terms, delivery of nutrient to and removal of waste products from the fetal circulation will be determined by a placentas' size, functional capability, rate of blood flow and differences in concentrations between the maternal and fetal circulation. The exact mechanism (s) by which each of these components are controlled is unknown, but undoubtedly include physical, hormonal and metabolic factors. Before discussing the effect of nutrition on placental growth and development, it is important to consider the interrelationships between the placenta and the fetus.

Changes in size and function of the placenta in the sheep precede the period of maximum fetal growth that occurs in the last trimester of pregnancy, which has been taken by some to indicate that placental weight can only be a crude index of the functional (transport) capacity of the placenta. However this does not appear to be the case, as placental size and function attained in mid pregnancy is linked with both early and later fetal growth. Foote et al. (1959) reported that as early as day 25 of pregnancy there was a significant association between fetal and membrane weight, and that by day 40 when maternal cotyledons could be measured there was an association between their weight and fetal weight. In our studies (Kelly and Newnham, unpubl. data), while we have found no significant relationship between placental weight and fetal weight at about day 70, by about day 90 differences of 100 g in weight of single fetuses were associated with 52 g (s.e. 14.8, $r = 0.65$, $P<0.01$) differences in placental weight. We have also found from real time ultrasound studies of placental growth and development, that placental weight at term was associated with placental measurements taken about the time that maximum size is obtained (days 70 to 80 of pregnancy, Kelly et al. 1987). Mellor et al. (1977), who ablated cotyledons at day 80 of pregnancy in twin bearing ewes, reducing the number by about 20%, found that at day 135 to 140 both fetal and placental weight were reduced and no evidence of hypertrophy of fetal placental tissue as occurs in the placentas of carunclectomised animals. The lack of compensatory growth by the fetal placenta was interpreted to suggest that placental limits to lamb birthweight are set before 80 days gestation. Similarly, removal of one of two fetuses at day 50 of pregnancy only results in partial compensation in placental weight (Vatnick et al. 1991). Evidence will be presented in this review to show that nutrition of the ewe in mid pregnancy affects placental growth and development, and that these changes affect fetal growth. Finally, there is a strong association between placental weight in late gestation and function (Bell 1984).

There is also evidence that the fetus can influence the placenta, through both effects of fetal sex (Alexander 1964), and fetal nutrient supply to the placenta (Charlton and Johengen 1987, Owens 1990, Hay 1991). Clearly the cooperation between the placenta and the fetus is important. Perhaps the best evidence of the inter relationships comes from human studies, where conditions that lead to disease or impaired functional capability of the placenta affect the growth potential of the fetus. The common disease pre-eclampsia occludes blood flow through the placenta and causes restricted growth of the fetus. However, disease states in which the fetus is primarily affected may not influence placental size; smoking is known to preferentially affect fetal and not placental growth (Newnham 1991).

III. PLACENTAL GROWTH AND DEVELOPMENT IN SHEEP AND HUMANS

The cotyledonary placenta of the sheep is formed by the attachment at about days 20-30 of pregnancy of the chorionic membrane to specific endometrial thickenings (caruncles) on the uterine wall. These points of attachment develop into bulb or round shaped cotyledons (also called placentomes) that can be easily imaged by real time ultrasound from about day 45 of pregnancy (Kelly et al. 1987). The bulb shape of many cotyledons changes to a flat button shape in late pregnancy as the fetal tissues envelop the maternal tissues (Alexander 1974). Maximum cotyledonary size and placental weight is reached at about day 70 to 80 of pregnancy (Kelly and Newnham 1990), after which it declines by up to 20% to term. Hay (1991) notes the lack of association between placental weight and function during gestation, with placental weight decreasing in late pregnancy in sheep while glucose transport capacity increases over eightfold. This change in functional capacity is in part due to a period of rapid increase in vascular development from about day 70 through proliferation within placental villi of blood vessels on both the maternal as well as fetal sides of the placenta (Stegeman 1974). Umbilical and uterine blood flow also increases in late pregnancy. These changes can be measured indirectly using Doppler ultrasound by recording the down stream resistance to blood flow in umbilical and maternal uterine arteries (peak systolic to least diastolic blood flow - S/D ratio; Newnham et al. 1987, Newnham et al. 1991).

In contrast to the cotyledonary placenta of the ewe, the human placenta is disc shape, and its growth and development more closely parallels that for the fetus (Hytten and Leitch 1971, Mellor 1987). The dimensions of the human placenta are not readily determined using real time ultrasound, and growth cannot be measured by any means. Studies on placental weight changes in humans invariably report changes that have been measured in only weight of the fetal component of the placenta. However vascular development can be measured indirectly as it can in sheep by Doppler ultrasound (Trudinger 1985).

IV. MATERNAL NUTRITION AND PLACENTAL WEIGHT IN SHEEP

There has been a considerable amount of work on placental growth and development in sheep, and the results of many of these studies are summarised in Table 1.

(a) Early pregnancy (to day 40 about)

Unlike the latter stages of pregnancy, the weight of published evidence on the effect of maternal nutrition about the time of establishment of placentation suggests that it does not have a major impact on placental size (Table 1). Even Foote et al. (1959) found in yearling ewes fed a limited ration from about the time of breeding had only 11% heavier maternal cotyledons (day 40) and 12% heavier fetal cotyledons (day 140) than animals fed on a full ration.

It is possible that maternal nutrition in early pregnancy could affect placental development indirectly through an effect on embryonic and early fetal mortality. Hinch et al. (1983) estimated that for a ewe with singles or twins, a difference in ovulation rate to lambs born of two would change lamb birthweight by about 6-10%. On the basis that a 560 g change in fetal weight at day 140 is associated with a 100 g change in placental weight (Kelly and Newnham 1990), a 6-10% change in birthweight is likely to be associated with about a 15% change in placental weight. Similar penalties were estimated by Rhind et al.(1980), who reported that the proportion of caruncles to which viable fetuses were attached fell within litter sizes as the number of ovulations rose above the number of fetuses. They estimated that when there was a decrease in number of cotyledons of the order of 50%, there would be a reduction of 32% in placental weight and a corresponding 16% reduction in fetal weight. However, it is by no means well established that the losses that affect birthweight are confined to early pregnancy (Kelly et al. 1989). So, while the birthweight reduction may be associated with lower cotyledon number due to the loss of other embryos, it is also likely that later fetal death, as occurs in ewes at higher ovulation rates, is a contributing factor.

Table 1. Summary of the effects of pregnancy nutrition on placental weights in sheep

Period of	Author	Day of pregnancy effect measured	Placental effect
Early pregnancy*			
	Clark and Speedy (1980)	90	no
	El-Sheikh et al. (1955)	40	no
	Foote et al. (1959)	40, 140	yes, L>H
	Parr et al. (1986)	90	no
Mid pregnancy			
	Clark and Speedy (1980)	90	no
	Davis et al. (1981)	137	yes, interact.
	De Barro et al. (1992)	90	yes, interact.
	Everitt (1964)	90	yes, H>L
	Faichney and White (1981)	135	yes, L>H
	Holst et al. (1992)	144	yes, H>L
	Kelly and Ralph (1988)	90	yes, H>L
	Kelly (1992)	90-100	yes, H>L
	Kelly et al. (1992)	100	yes, H>L
	McCrabb et al. (1986)	96	yes, H>L
		142	no
	McCrabb et al. (1991)	96, 140	yes, L>H
	McCrabb et al. (1992a)	96	yes, L>H, H>L
	McCrabb et al. (1992b)	96, 140	yes, H>L
	Rattray and Trigg (1979)	135	yes, H>L
Late Pregnancy			
	Faichney and White (1981)	135	no
	Holst et al. (1992)	144	no
	Mellor (1983)	142	yes, H>L
	Rattray and Trigg (1979)	135	no

* includes treatments prior to or about joining
L = low nutrition, H = high nutrition

(b) <u>Mid pregnancy, from day 40 to about day 100</u>

Of the 16 sets of experiments published in the 13 papers reviewed, in only two was there no significant effect of differential nutrition in mid pregnancy on placental weight. Clearly maternal nutrition in mid pregnancy can affect placental growth, the general consensus being that a high plane of feeding increases placental size (nine experiments). However in three experiments the low plane of nutrition ewes had heavier placentas, and in the other two data sets there were interactions between plane of nutrition in mid and late pregnancy or starting body weight and placental response. There are many possible explanations for this variation between studies, largely related to differences outside the experimental design such as:

- variation in extent and duration of differential nutrition
- variation in management from cessation of differential feeding to measurement
- differences in sheep breeds and mature body sizes
- variation in exercise levels for the ewes - animals run inside in pens versus outside grazing in paddocks
- ambient temperature
- different numbers of fetuses - singles v twins
- age of ewe
- body weight and condition score at the start of the experiment.

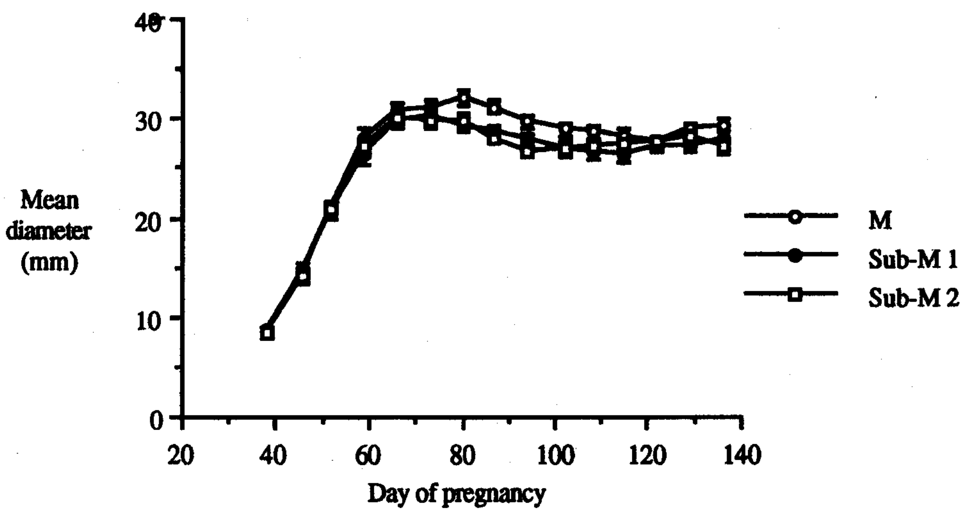
Added to this extensive list of possible confounding factors must also be the lack of experimental robustness of some of the work reported. Analyses of my own data show that at least 10 animals per treatment would be required to pick a difference of 0.1 kg (i.e. about 20%) in placental weight. Some of the studies reported fall considerably short of this number, and it is only because of low variation between animals within treatments in some cases that significant effects are recorded.

Perhaps the most conjecture in the last decade as to the effect of maternal nutrition on placental development arises from the possible influence of starting condition of the ewe. The publications reviewed suggest that ewes in low to moderate condition have a different response to those in good condition.

(1) Response of ewes in low to moderate condition With respect to ewes in low to moderate condition (condition score of 3 or less on a 1-5 scale), the weight of evidence points to a reduction in placental weight by underfeeding in mid pregnancy. I and my colleagues have conducted several experiments studying the effect of differential nutrition in mid pregnancy (maintenance [M] v. 0.3 maintenance [Sub-M]) on placental growth and development in adult Merino ewes bearing one or two fetuses (n = 10-15 ewes). The ewes were all housed in individual pens, and started the experiments in moderate condition (score 2.5 to 3) and weighing 43-46 kg. In late pregnancy the ewes were either fed at M or 2M. Placental development was followed regularly by ultrasound recording of changes in mean cotyledon diameter and umbilical and maternal arterial resistance to blood flow (Kelly et al. 1987, Newnham et al. 1987). Ewes were slaughtered at either around day 95 or 140 of pregnancy, and placental measurements recorded. Details of experimental design are contained in Kelly et al. (1989).

The mean diameter of the cotyledons increased to about day 70 of pregnancy, followed by a marginal decline to day 136 (Fig. 1). The effect of underfeeding was not evident until about the time that maximum cotyledon diameter was obtained. The Sub-M treatment ewes had significant lower ($P<0.05$ to $P<0.001$) mean cotyledon diameters compared with the M treatment ewes from day 80 to 102 of pregnancy. These differences were of the order of 1.8 to 3.1 mm in mean cotyledon diameter. While placental weights were not measured at about day 90 in this experiment, an estimate of placental weight can be obtained by using the relationship between mean cotyledon diameter measured by ultrasound and placental weight on day 90 generated from other data (1 mm difference in mean cotyledon diameter of ewes with a single fetus = 26 g [s.e. = 7.4] difference in placental weight). The differences in estimated placental weights were of the order of 66 g to 80 g. This means that the M fed ewes had an estimated placental weight about 17% heavier than the Sub-M ewes. By day 138 of pregnancy the differences between these two treatments when the ewes were fed to maintenance in late pregnancy was 70 g (sed = 44.1, p = 0.12) or 16%. Changes recorded in ewes bearing two fetuses follow a similar pattern, with significant differences again being detected about the time that maximum cotyledon diameters were attained. Field studies (Kelly et al. 1992) have found differences in mean cotyledon diameter of the order of 2.6 mm between maintenance and severely underfed ewes, giving estimated differences in placental weights of the order found in the animal house studies. In commercial flocks (Kelly 1992) there appears to be an even greater variation in placental weights, since the range between 15 flocks in mean cotyledon diameter for twin bearing ewes was of the order of 4.6 mm, giving an estimated range in placental weights of 150 g. This greater range was largely associated with both ewe liveweight at the end of joining ($P<0.001$) and weight change from the end of joining to mid pregnancy ($P<0.01$), with the model including both variables explaining 71% of the between flock variation in estimated placental weight.

Fig. 1. Changes in cotyledon diameter during pregnancy in single bearing ewes



In comparison with the consistent effects on placental weight, the effect of maternal undernutrition on the development of both fetal and maternal vasculature of the placenta has been variable. Development of the vasculature has been studied using Doppler ultrasound. In the animal house experiments reported above, the M ewes bearing one fetus had greater umbilical S/D ratios on days 94 to 115 of pregnancy than the Sub-M ewes, but the difference was only significant for one of two Sub-M groups. Maternal S/D ratios were also greater in the M ewes than the Sub-M group on days 73 to 87 and 122 of pregnancy, but again the difference was only significant when compared with one of the two Sub-M groups. For ewes bearing two fetuses, no significant difference between feeding treatments in maternal or fetal S/D ratios has been detected (Newnham et al. 1991). In contrast, in the field studies lower maternal S/D ratios have been recorded in the maintenance fed ewes bearing one or two fetuses (Kelly et al. 1992) and the mortality rate of twins is positively associated with S/D ratio (Kelly 1992). The latter findings reflect a penalty from poorer feeding conditions, whereas the animal house studies with singles suggest a compensatory mechanism exists in some underfed ewes to overcome the lower placental weight induced by underfeeding in mid pregnancy.

(2) Response of ewes in high condition score There are several studies which suggest that there may be an effect of starting condition of the ewe on her response to mid pregnancy

nutrition. McCrabb et al. (1992a) found that the response of ewes to a similar level of underfeeding as I have used in my animal house studies resulted in a decrease in placental weight in the first year, and an increase in the second year, in comparison to ewes fed at about maintenance. The only initial difference noted between the two years was liveweight of the ewes at mating, being heavier in year 2. However, there were differences between the two years in the way the animals were managed, so it is possible that the differences recorded resulted from the different conditions under which the animals were run.

In other studies, McCrabb et al. (1992b) have found that prolonged underfeeding from days 30 to 96 of pregnancy reduced placental weight, but shorter periods of restriction (50-96, 75-96 days) did not. While they concluded that feed restriction during days 30-50 of pregnancy is critical, they also suggested that placental growth during the later stages of mid-pregnancy would be more sensitive to maternal restriction in conditions where the ewes have severely depleted body reserves. My data indicates that effects on cotyledon diameter are only detectable after about day 70, which indicates that the effect becomes evident at this time, but it does not assist in delineating the period or conditions under which the placenta is sensitive to changes in the ewes nutrition.

There is some further evidence on the effect of ewe condition on placental growth. De Barro et al. (1992) reported that when Merino cross ewes were fed to achieve two liveweights at mating (63 and 51 kg), and then differentially fed from days 30 to 90 of pregnancy, the response was affected by mating liveweight. For the single bearing ewes, undernutrition over mid-pregnancy increased placental weight at day 90 in the light and decreased placental weight in the heavy ewes (interaction $p = 0.06$). For twin bearing ewes the responses were not significant, but the lighter ewes had heavier placentas.

In summary, the results at best can be regarded as equivocal for an effect of ewe condition on their placental response to mid pregnancy nutrition.

(c) Late pregnancy, from about day 100 to 140

While there is some evidence that underfeeding over this period will affect placental weight at about day 140, the data generally supports the conclusion that the effect is negligible or at best small. Mellor (1983) reports that in one group severe underfeeding from days 112 to 131 of pregnancy reduced placental weight, whereas two other groups severely underfed either from either days 112 to 142, or from days 95 to 116, had no significant decrease in placental weights. Holst et al. (1992) found no significant effect of restricted feeding for 28 days from days 87 or 95 of pregnancy on cotyledon weight at day 144. I have found no significant effect of feeding single bearing ewes at 0.5 times maintenance in late pregnancy on placental weight at day 140 (Kelly and Newnham 1992). Davis et al. (1981) also recorded no significant differences in fetal placental weight at day 137 in ewes fed at different rates in late pregnancy.

V. CONCLUSION

Nutrition of the ewe during mid pregnancy can affect placental growth and development, while nutrition at other times during pregnancy does not appear to have any marked effect. The direction of the response to mid pregnancy undernutrition may be affected by the condition/liveweight of the ewes when they enter the experimental program, with some evidence to suggest that those in very good condition or high liveweights may have heavier placentas than their well fed counterparts. While the outcome of changes in the placenta have been evaluated in terms of effects on birthweight and newborn survival, increasing attention is now being focused on effects on quality of adult life. To this end, studies have recently been initiated on the effects of maternal undernutrition on wool quality in the resultant progeny (Kelly, R.W. unpubl. data), and relationships between resistance to blood flow and adult performance in humans (Newnham, J.P. unpubl. data).

REFERENCES

ALEXANDER, G. (1964). J. Reprod. Fert. 7: 289.
ALEXANDER, G. (1974). In 'Size at Birth', p 215, eds K. Elliot and J. Knight. (Elsevier: Amsterdam).
BARKER, D.J.P. (1990). Brit. Med. J. 301: 1111.
BELL, A.W. (1984). In 'Reproduction in Sheep', p 144, eds D.R. Lindsay and D.T.Pearce (Australian Academy of Science: Canberra).
CHARLTON, V. and JOHENGEN M. (1987). Pediatric Res. 22: 55.
CLARK, C.F.S. and SPEEDY, A.W. (1980). Anim. Prod. 30: 485.
DAVIS, S.R., RATTRAY, P.V., PETCH, M.E. and DUGANZICH, D.M. (1981). Proc. N.Z. Soc. Anim. Prod. 41: 218.
De BARRO, T.M., OWENS, J., EARL, C.R. and ROBINSON, J.S. (1992). In 'Fetal and Neonatal Workshop', Monash University, Paper No. 18.
EL-SHEIKH, A.S., HULET, C.V., POPE, A.L. and CASIDA, L.E. (1955). J. Anim. Sci. 14: 919.
EVERITT, G.C. (1964). Nature, Lond. 201: 1341.
FAICHNEY, G.J. and WHITE, G.A. (1987). Aust. J. Biol. Sci. 40: 365.
FOOTE, W.C., POPE, A.L., CHAPMAN, A.B. and CASIDA, L.E. (1959). J. Anim. Sci. 18: 463.
HAY, W.W. (1991). Proc. Nut. Soc. 50: 321.
HINCH, G.N., KELLY, R.W., DAVIS, G.H., OWENS, J.L. and CROSBIE, S.F. (1985). Anim. Reprod. Sc.. 8: 53.
HOLST, P.J., ALLAN, C.J. and GILMOUR, A.R. (1992). Aust. J. Agric. Res. 43: 315.
HOLST, P.J., KILLEEN, I.D. and CULLIS, B.R. (1986). Aust.J.Agric.Res. 37: 647.
HYTTEN, F.E. and LEITCH, I. (1971). 'The Physiology of Human Pregnancy' 2nd edn (Blackwell Scientific Publications: Oxford, London & Edinburgh).
KELLY, R.W., (1992). Aust. J. Agric. Res. 43: (in press).
KELLY, R.W. and NEWNHAM, J.P. (1990). In 'Reproductive Physiology of Merino Sheep - Concepts and Consequences', p 161, eds C.M. Oldham, G.B. Martin and I. Purvis. (The University of Western Australia: Perth).
KELLY, R.W. and NEWNHAM, J.P. (1992). Proc. Aust. Soc. Anim. Prod. 19: 201.
KELLY, R.W., NEWNHAM, J.P., JOHNSON, T. and SPEIJERS, E.A. (1987). Aust. J. Exp. Agric. 38: 757.
KELLY, R.W. and RALPH, I.G. (1988). Proc. Aust. Soc. Anim. Prod. 17: 218..
KELLY, R.W., SPEIJERS, E.J., RALPH, I.G.and NEWNHAM, J.P. (1992). Aust.J.Exp.Agric. 43:339.
KELLY R.W., WILKINS, J.F. and NEWNHAM, J.P. (1989). Aust. J. Exp. Agric. 29: 339.
McCRABB, G.J., HOSKING, B.J. and EGAN, A.R. (1986). Proc. Nutr. Soc. Aust. 11: 147.
McCRABB, G.J., HOSKING, B.J. and EGAN, A.R. (1992b). Aust. J. Agric. Res. 43: (in press).
McCRABB, G.J., EGAN, A.R.and HOSKING, B.J. (1991). Brit. J. Nutr. 65: 157.