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THE EFFECT OF ALTERATIONS IN PLACENTAL BLOOD FLOW ON THE GROWTH OF AND NUTRIENT SUPPLY TO THE FETAL GUINEA-PIG

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SUMMARY

1. The distribution of the cardiac output and the maternal placental blood flow has been measured in guinea-pigs at days 49–51 of pregnancy using radioactively labelled microspheres. In some instances uterine blood flow was reduced chronically by ligating one uterine artery at day 30 of pregnancy.

2. Between 3 and 4 % of the cardiac output passed normally to placenta, and this could be reduced to < 2 % after uterine artery ligation. The result of the ligation was to reduce fetal and placental weight by up to 70 %.

3. Fetal and placental weight showed a close linear correlation in controls and in pregnancies with uterine artery ligation. However, when placental size was reduced below 60 % of control, fetal weight was less affected by a reduction in placental weights than normal.

4. Placental blood flow and placental size exhibited a close linear relationship over the whole range of values, but there was limiting placental weight which approached 1·3 g as placental blood flow approached zero. Thus a reduced placental size, particularly below about 50 %, was associated with a proportionately greater reduction in maternal placental blood flow.

5. Maternal placental blood flow or the percentage of maternal cardiac output to the placenta and fetal weight also showed a well-correlated linear relationship. However, when placental blood flow was below about 50 % of control values further reduction had a less than normal effect upon fetal growth.

6. Small fetuses were hypoglycaemic and hypoinsulinaemic and the degree of each was dependent upon the extent of the reduction in fetal weight and in maternal placental blood flow. In fetuses that were below about 40 % of normal size, and in which placental blood was below about 30 % of control, fetal weight was less sensitive to falls in blood glucose, which in turn was more sensitive than normal to a fall in maternal placental blood flow.

7. The results indicate that over the range of 50–100 % of normal fetal growth, maternal placental blood flow and probably nutrient supply to the fetus vary in parallel. Hence over this range fetal and placental growth rates are determined in

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part by placental blood flow. At placental blood flow rates and fetal growth rates below 40% of normal fetal growth is less dependent upon placental blood flow than usual, presumably because of a reduced dependence upon glucose metabolism for growth. This would appear to be essential, since as maternal placental blood flow is reduced to low values the placenta has to utilize an increasing proportion of the available glucose.

INTRODUCTION

At any particular gestational age a close relationship between fetal and placental weight has been observed for a wide range of species (Alexander, 1964; Van Den Berg & Yerushalmy, 1966; McLaren, 1965; Thomson, Billewicz & Hytten, 1969; Kulhanek, Meschia, Makowski & Battaglia, 1974; Bruce & Abdul-Karim, 1973; Wootton, McFadyen & Cooper, 1977; Lafeber, Jones & Rolph, 1979). The quantitative nature of this relationship changes with gestational age (Bruce & Abdul-Karim, 1973; Stegemen, 1974; Rosenfeld, Morriss, Makowski, Meschia & Battaglia, 1974). There is also, in selected species at a particularly gestational age, a close relationship between fetal weight and maternal placental blood flow (Duncan & Lewis, 1969; Leduc, 1972; Bruce & Abdul-Karim, 1973; Rosenfeld *et al.* 1974; Wooton *et al.* 1977; Gilbert & Leturque, 1982). The underlying physiological reasons for this close relationship have not been provided but it is assumed, not unreasonably, that the size of the placenta is a reflexion of its transport capacity and that this nutritive function is a major determinant of fetal growth. However, it is important to note that if such an explanation is correct it is likely that it is the reduction in placental size rather than that in maternal placental blood flow that is responsible primarily since, in the sheep at least, large short-term reductions in placental blood flow do not necessarily depress glucose transfer to the fetus (Simmons, Battaglia & Meschia, 1979). Moreover placental size and blood flow need not necessarily be related closely (Rosenfeld *et al.* 1974).

An alternative method of studying the relationship between placental and fetal growth is to reduce both by depressing uterine artery blood flow through ligation (Wigglesworth, 1964; Lafeber *et al.* 1979; Gilbert & Leturque, 1982). This causes reduced placental and fetal growth more or less in proportion although the quantitative nature of the relationship does change with larger degrees of growth restriction (Lafeber *et al.* 1979). Paradoxically, Bruce (1977) has reported for the pregnant rat that uterine artery ligation, while slowing the growth of the fetus, does not cause a significant fall in placental blood flow. However, in these studies the fetuses from the horn with a ligated uterine artery were pooled, despite wide variation in fetal size. If these data are correct it is difficult to explain the mechanism of reduced placental growth after uterine artery ligation or to provide the reasons for the fetal hypoglycaemia and associated indications of depressed placental transport (Jones & Robinson, 1979).

Fetal hypoglycaemia is a common condition associated with intra-uterine growth retardation (Roux, Tordet-Caridroit & Chanez, 1970; Jones & Robinson, 1979; Lafeber *et al* 1979; Jones, Harding, Robinson, Lafeber & Rolph, 1981). This and the low fetal insulin concentration and poor placental transfer of glucose after maternal infusion (Girard, Chanez, Kervan, Tordet-Caridroit & Assas, 1976; Jones & Robinson,

1979; Robinson, Hart, Kingston, Jones & Thorburn, 1980; Jones *et al.* 1981) are indicative of reduction in both placental transport of and fetal consumption of glucose.

The importance of this is shown by the relatively close relationship between fetal size and fetal plasma glucose concentration observed in fetal sheep and guinea-pigs with restricted intra-uterine growth rates (Jones *et al.* 1981; Jones, Lafeber, Rolph & Fellows, 1980). Despite these central questions about the nature of the control of fetal growth we have no clear-cut data on the relationship between maternal placental blood flow, fetal and placental growth and the rate of nutrient supply to the fetus in growth retardation states. The fact that, despite a reduction in fetal and placental weight more or less in proportion, fetuses are hypoglycaemic and appear to have a reduced glucose consumption per unit body weight, indicates that placental transport capacity may be reduced to a greater extent than the fall in weight indicates.

To help resolve some of these uncertainties the present study reports the relationship of placental and fetal growth and fetal glucose concentration to maternal placental blood flow in guinea-pigs subjected to uterine artery ligation.

METHODS

Guinea-pigs of the Dunkin–Hartley strain were used and the date of mating determined as described by Elvidge (1972). On day 30 of pregnancy guinea-pigs were anaesthetized with sodium pentobarbitone (30 mg/kg, I.V.). Under aseptic conditions an incision of about 2 cm in the abdominal wall close to the umbilicus was made. This allowed the exposure of the mesometrial fat pad of one uterine horn in which one uterine artery was imbedded. This uterine artery was ligated near the cervical end of the arterial arcade with a silk ligature (No. 1, Mersilk, Ethicon, Edinburgh). (In sham-operated females the uterine artery was exposed but no ligature was placed around it.) Then the abdominal wall and the skin were closed separately by stitching. For fetal survival it was essential that this surgery lasted no more than 15–20 min. The animals recovered within 1–2 hr.

A second operation under sodium pentobarbitone anaesthesia (30 mg/kg, I.V.) was carried out 7–9 days before flow studies at 49–51 days. Under aseptic conditions a polyethylene catheter (i.d., 0·78 mm) was inserted through the carotid artery into the left ventricle. A second catheter, made by 'drawing out' the polyethylene tubing, was inserted via the femoral artery into the distal aorta. Both catheters were passed subcutaneously to the back of the neck. They were filled with heparin in 0·9 % (w/v) NaCl (250 u./ml.) and plugged. Every 48 hr they were flushed with heparin solution.

On the day of study the pregnant guinea-pigs were placed in an open box in a quiet laboratory and a continuous recording of heart rate and blood pressure made. After about one hour these recordings became stable. Blood was withdrawn with a Braun infusion pump at 1 ml./min for 2 min. After 10 sec of blood withdrawal, 0·3 ml of a suspension of sonicated ^{46}Sc 15 μm microspheres (3M Company) were infused into the left ventricle and flushed in with 1 ml. of 0·9 % (w/v) NaCl. This process took 50 sec. The arterial reference sample was drawn as described above and placed directly into a counting vial.

At this point the guinea-pig was anaesthetized with sodium pentobarbitone (30 mg/kg, I.V.) and blood samples (up to 0·7 ml.) were withdrawn from the umbilical vein of the small and of the control fetus. The fetus, uterus and placenta were weighed and fetal and maternal tissues were then dissected. Radioactivity in the dissected tissues was determined in a Packard 5320 γ-counter. In this instrument sample geometry within the counting vials does not influence the total count by more than ± 2 %. Each guinea-pig received between $6{\cdot}5 \times 10^6$ and 15×10^6 microspheres. Blood flows and cardiac output were calculated essentially as follows:

$$\dot{Q}_{\text{flow}} = \frac{\textit{spheres in organ} \times 1\ \textit{ml./min}}{\textit{spheres withdrawn from aorta}},$$

and the cardiac output was calculated as:

$$\dot{Q}_{\text{CO}} = \Sigma \dot{Q}_{\text{flow}}.$$

TABLE 1. The effect of uterine artery ligation on placental blood flow, uterine blood flow and fetal growth in the guinea-pig

	Control horn		Sham-operated horn		Ligated horn (A)		Ligated horn (B)	
	Fetus 1	Fetus 2	Fetus 1	Fetus 2	Fetus 1	Fetus 2	Fetus 1	Fetus 2
n	24		6		12		12	
Fetal weight (g)	35·6 ± 2·1	33·1 ± 1·4	34·9 ± 1·7	32·6 ± 1·2	12·6 ± 2·2	20·4 ± 1·7	18·8 ± 2·9	31·3 ± 2·4
Maternal cardiac output (ml./min)	462 ± 157		443 ± 182		437 ± 142		487 ± 168	
Placental weight (g)	3·51 ± 0·27	3·32 ± 0·30	3·52 ± 0·21	3·24 ± 0·28	1·81 ± 0·26	2·29 ± 0·24	2·37 ± 0·24	3·06 ± 0·31
Placental blood flow								
(ml./min)	15·8 ± 3·7	15·6 ± 3·9	15·5 ± 2·6	14·2 ± 3·7	4·1 ± 1·3	8·43 ± 2·0	8·9 ± 2·2	15·1 ± 3·5
(ml./min . g)	4·51 ± 0·26	4·67 ± 0·24	4·40 ± 0·40	4·39 ± 0·35	2·27 ± 0·23	3·68 ± 0·28	3·76 ± 0·31	4·95 ± 0·40
Cardiac output (%)	3·43 ± 0·51	3·37 ± 0·32	3·50 ± 0·42	3·21 ± 0·34	0·94 ± 0·26	1·93 ± 0·18	1·83 ± 0·22	3·11 ± 0·45
Uterine weight (g)	5·2 ± 2·7		4·8 ± 1·6	3·9 ± 2·0	4·4 ± 1·8		4·7 ± 2·0	
Uterine blood flow								
(ml./min)	3·2 ± 1·5		2·7 ± 0·9	2·5 ± 1·0	1·4 ± 0·6		1·9 ± 0·65	
(ml./min . g)	0·62 ± 0·23		0·56 ± 0·18	0·64 ± 0·20	0·32 ± 0·12		0·40 ± 0·17	
Cardiac output (%)	0·69 ± 0·18		0·61 ± 0·15	0·57 ± 0·20	0·33 ± 0·11		0·39 ± 0·15	

Results are means ± S.D. In each case the observations were restricted to those animals with two fetuses in each uterine horn. For the sham-operated horn fetus 1 was taken from the manipulated horn and fetus 2 came from the control horn, both at the base of the uterus. In all other instances fetus 1 and 2 came from the same horn, 1 being adjacent to the ligation on the uterine artery. The fetuses from the ligated horns have been divided arbitrarily into two groups, A containing very small fetuses and B containing fetuses around half the normal body weight. Pregnant guinea-pigs were ligated at day 30 of pregnancy and measurements were made at days 49–51 of pregnancy.

Plasma glucose was measured as previously described (Jones, 1977). The insulin concentration in fetal plasma was determined by radioimmunoassay, using guinea-pig insulin prepared by Dr Steve Wood (Birkbeck College, London) and an anti-guinea-pig insulin antibody prepared by Dr M. Lazarus (Wellcome Research Laboratories, Dartford, Kent). Guinea-pig insulin was labelled with Na ^{125}I essentially as described by Greenwood, Hunter & Glover (1963) and separated from Na ^{125}I by Sephadex G-25 chromatography on a 0·5 × 10 cm column. Plasma samples were diluted in 0·1 M-sodium potassium phosphate (pH 7·4) and to 0·1 ml. of this was added 0·1 ml. of antiserum

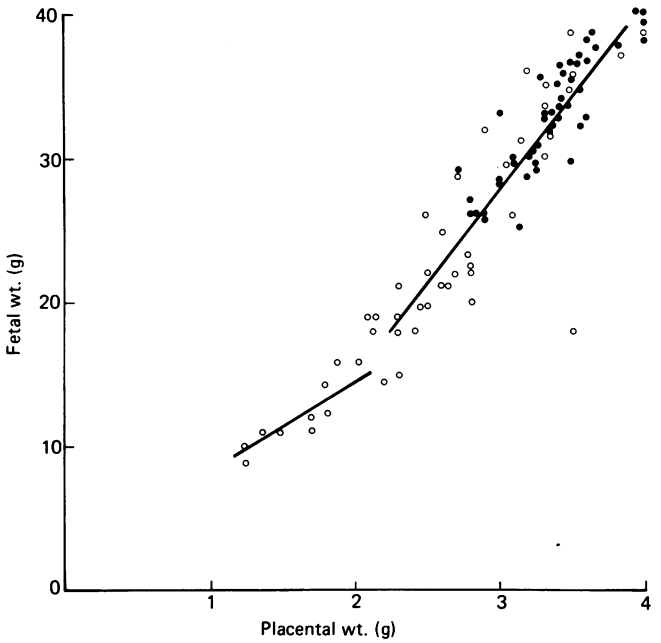

Fig. 1. The relationship between placental weight and fetal weight in guinea-pigs at days 49–51 of pregnancy. Results are from normal pregnancies (●) and from those in which a uterine artery was ligated (○) at day 30 of pregnancy.

(1/8000) diluted in the phosphate buffer. This was left for 6 hr at 4 °C then 0·1 ml. of ^{125}I-labelled insulin was added and the incubation continued overnight at 4 °C. Free and bound hormone were separated by adding 0·1 ml. of sheep serum followed by 0·5 ml. of 1·5% (w/v) glycine (pH 7·4) containing 0·25% (w/v) Dextran T-70 and 0·5% (w/v) Norit A charcoal. After mixing this was left for 30 min at 4 °C and the charcoal pellet precipitated by centrifugation and counted in an LKB 8 counter. Assays and unknowns were run in triplicate and detected between 0·5 and 50 ng/ml. The inter-assay coefficient of variation at 5 pg/ml. was 12·4 ± 2·9% (6) and the value for the intra-assay variation was 9·8 ± 2·1% (6).

Where appropriate, results are expressed as means ± S.D. with the number of observations in parenthesis. Statistical significance was determined by the Student's *t* test.

RESULTS

Fetal and placental weight

Ligation of the uterine artery in pregnant guinea-pigs at day 30 of pregnancy produces growth retardation in fetal guinea-pigs by day 50 of gestation (Lafeber *et al.* 1979). The degree of retardation was highly variable, but such fetuses at placental sites adjacent to the ligation can be divided arbitrarily into two groups: those that were about 27–38% of normal weight and those that were 45–60% of normal weight

TABLE 2. The distribution of the cardiac output in guinea-pigs at days 49–51 of pregnancy

		Flow		
	Weight (g)	(ml./min)	(ml./min.g)	Cardiac output (%)
Heart	2·24±0·27	21·2±3·9	9·5±1·8	4·7±0·91
R. kidney	2·37±0·19	20·3±3·6	8·7±1·5	4·5±1·1
L. kidney	2·26±0·21	21·2±4·2	9·4±2·0	4·7±1·3
R. ovary	0·59±0·010	0·37±0·08	6·3±1·1	0·081±0·014
L. ovary	0·56±0·011	0·40±0·09	7·1±1·9	0·088±0·016
R. brain	1·86±0·21	5·9±1·1	3·2±0·27	1·3±0·10
L. brain	1·92±0·16	5·6±0·9	2·9±0·43	1·25±0·11
R. adrenal	0·21±0·043	0·34±0·06	1·6±0·37	0·075±0·025
L. adrenal	0·23±0·065	0·42±0·07	1·8±0·46	0·094±0·018
Lung	3·56±0·46	19·8±4·6	5·6±0·1	4·4±0·52
Spleen	2·19±0·34	8·8±2·3	4·0±0·72	1·95±0·36
Liver	26·4±3·9	0·68±0·17	0·026±0·005	0·15±0·031

Results are means ±S.D. of twenty-four measurements. Ligation was placed on the left uterine artery. R., right; L., left.

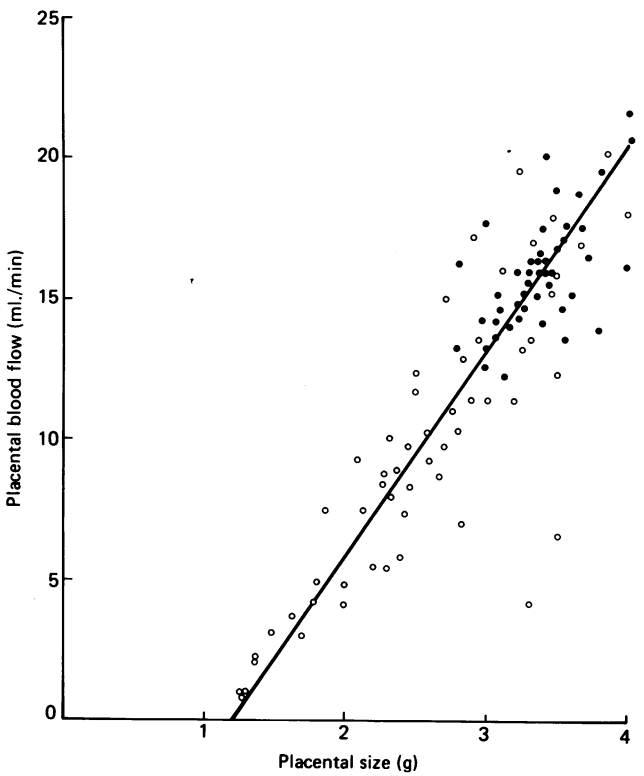

Fig. 2. The relationship between placental weight and maternal placental blood flow in guinea-pigs at days 49–51 of pregnancy. Results are from normal pregnancies (●) and from those in which a uterine artery was ligated (○) at day 30 of pregnancy.

(Table 1). Fetuses (fetus 2) separated by one placental site from the ligation (i.e. on the ovarian side) were also smaller than normal, but less so than those immediately adjacent to the ligation. The weight of fetuses in uterine horns subjected to sham operations was normal (Table 1). In most instances the reduction in fetal weight was

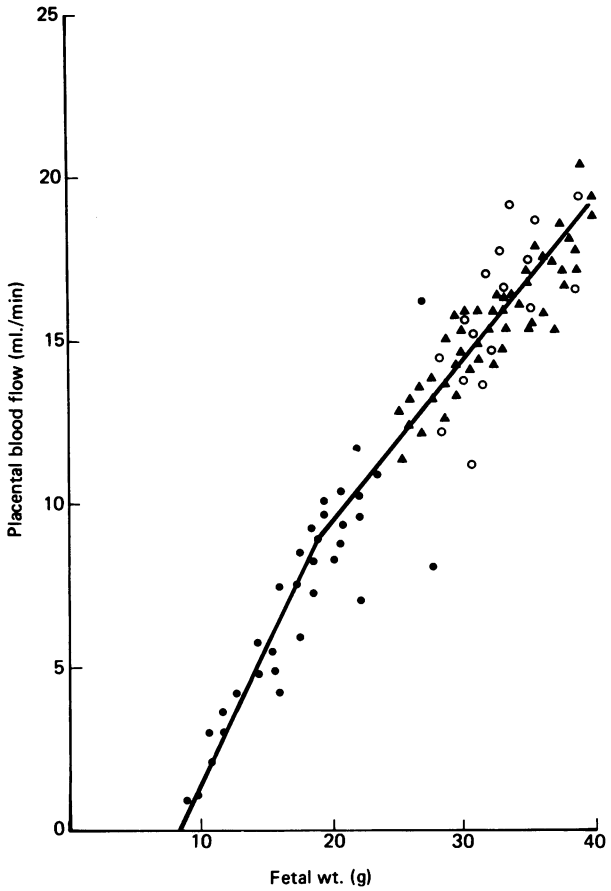

Fig. 3. The relationship between fetal weight and maternal placental blood flow in guinea-pigs at days 49–51 of pregnancy. (▲), non-ligated uterine horn, normal size; (○), ligated horn, normal size; (●), ligated horn, reduced size. Uterine artery ligation was carried out at day 30 of pregnancy.

associated with a proportional reduction in placental weight (Table 1 and Fig. 1) and a close relationship between the two was maintained over a fetal weight range of 2–4 g (Fig. 1). In the very small fetuses, when fetal weight falls below 17 g and placental weight falls below about 2·2 g the relationship between the two alters. At this degree of growth retardation, a reduction in placental size caused a smaller fall in fetal size than was normal.

Placental blood flow

Data on the distribution of the cardiac output is given in Table 2. The even distribution of microspheres to both sides of the body indicates that there was good

mixing of microspheres in the heart and no evidence of streaming was found. The cardiac output of the control guinea-pigs and those subjected to uterine artery ligation was the same (Table 1) and no difference in the distribution of the cardiac output to any tissues other than the uterus and placenta was observed. Placental blood flow was reduced by uterine artery ligation (Table 1) and the extent of this

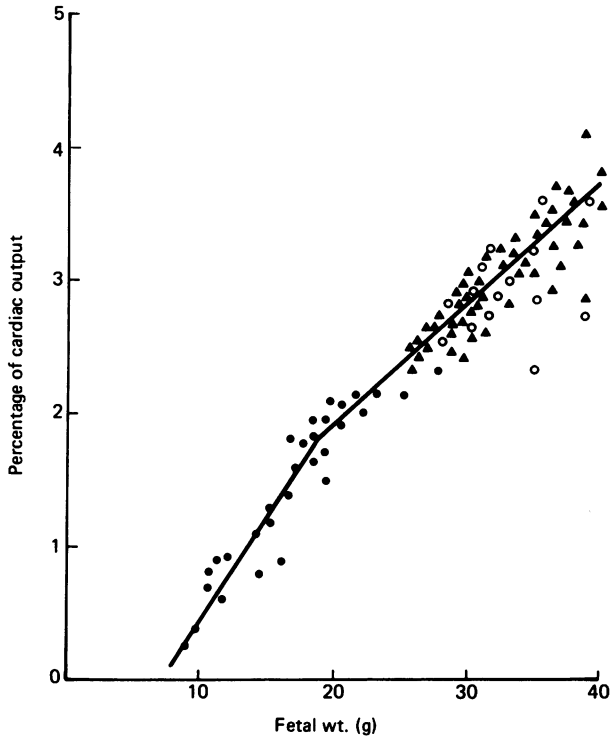

Fig. 4. The relationship between maternal cardiac output and fetal weight in guinea-pigs at days 49–51 of pregnancy. (▲), non-ligated uterine horn, normal size; (○), ligated uterine horn, normal size; (●), ligated uterine horn, reduced size. Uterine artery ligation was carried out at day 30 of pregnancy.

fall was correlated closely with the reduction of placental weight over a wide range of flows (Fig. 2). However, in the group of very small fetuses the placental blood flow/g of placenta was about one-half of normal (Table 1).

Placental blood flow (Fig. 3) and the percentage of the cardiac output going to the placenta (Fig. 4) showed the same biphasic relationship with fetal weight as did placental weight. Thus at fetal weight of less than 20 g and a placental flow of less than 9 ml./min or less than 2 % of the cardiac output reduction in flow had a smaller than normal effect upon fetal weight.

Nutrient supply to the fetus

The plasma insulin concentration in the control fetuses was $13{\cdot}6 \pm 4{\cdot}1(20)$ ng/ml. by comparison with a value of $4{\cdot}6 \pm 1{\cdot}0$ (6) ng/ml. ($P < 0{\cdot}001$) in the fetus of about 34 % of normal weight and a value of $2{\cdot}1 \pm 0{\cdot}8$ (6) ng/ml. ($P < 0{\cdot}001$) in fetuses of about 43 % normal weight.

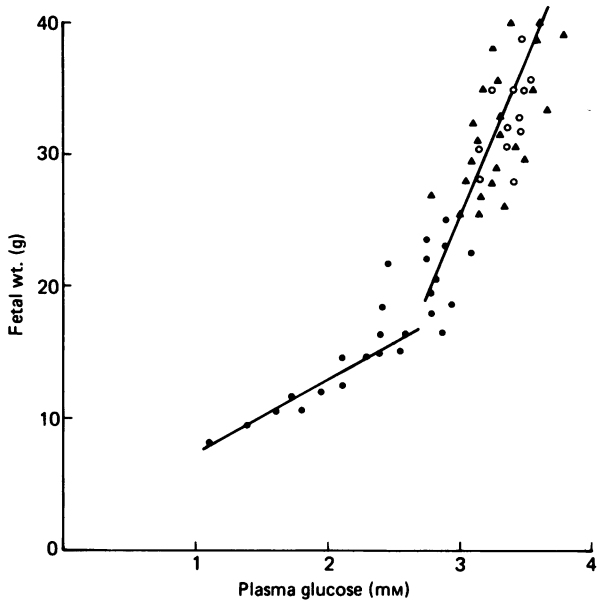

Fig. 5. The relationship between fetal weight and glucose concentration in umbilical venous plasma at days 49–51 of pregnancy. The fetuses were from (▲), non-ligated uterine horns; (○), ligated horns, normal size; (●), ligated horns, reduced size. Uterine artery ligation was carried out at day 30 of pregnancy.

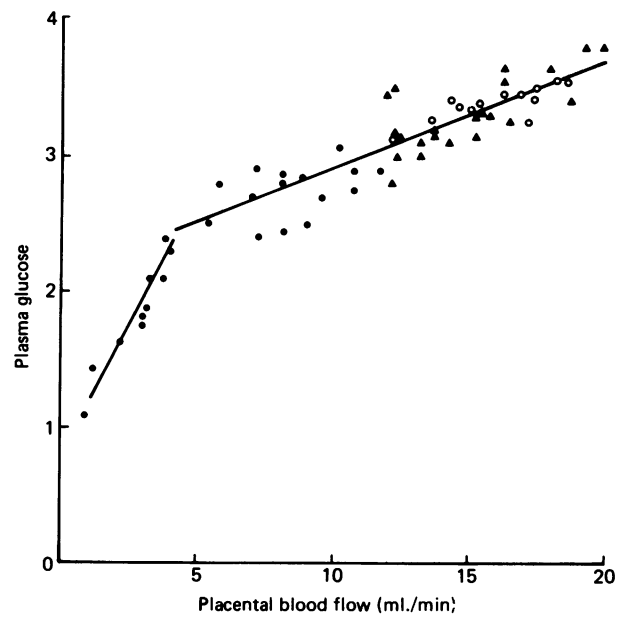

Fig. 6. The relationship between maternal placental blood flow and glucose concentration in umbilical venous plasma at days 49–51 of pregnancy. Fetuses were from (▲), non-ligated uterine horn, normal size; (○), ligated horn, normal size; (●), ligated horn, reduced size. Uterine artery ligation was carried out at day 30 of pregnancy.

There was a relationship between plasma glucose concentration and fetal weight, although between fetal weights of 18 and 40 g the variation in fetal plasma glucose concentration was small (Fig. 5). For fetuses of less than about 18 g there was also a close relationship between fetal weight and fetal plasma glucose concentration, but here a reduction in plasma glucose was associated with an almost proportional reduction in fetal weight.

A similar picture was seen in the relationship between placental blood flow and fetal plasma glucose concentration (Fig. 6). Thus below a placental flow of 5 ml./min reduction in flow was associated with a much larger fall in plasma glucose than normal.

DISCUSSION

In the present studies the initial surgery to cause restriction of fetal growth was conducted 20 days before the measurements upon the distribution of the maternal cardiac output and upon the fetus. Thus there did not appear to be any effect of the surgery alone, without arterial ligation, upon the growth of the fetus. This is not always true of studies on the pregnant rat, the other species in which the effects of uterine artery ligation have been studied. Thus in this species the surgery for ligation is usually only a few days before fetal and maternal measurements are made and effects of surgery alone are apparent (Kollee, Monnens, Trijbels & Veerkamp, 1981). Moreover the measurements reported here on the maternal cardiac output were made upon the unrestrained, unanaesthetized guinea-pig, and usually such measurements upon small pregnant animals are made under anaesthesia (Duncan & Lewis, 1969; Leduc, 1972; Bruce & Abdul-Karim, 1973; Wooton *et al.* 1977; Gilbert & Leturque, 1982). This may explain why the maternal placental blood flows reported here at about 4·5 ml./g of placenta are considerably higher than those reported for the pregnant rabbit, pig and rat. Thus it has been shown that sodium pentobarbitone, the anaesthetic normally used with small animals, leads to reduced cardiac output and blood flow to the viscera (Smith & Hutchins, 1980; Sasaki & Wagner, 1971).

The studies show, in contrast to those of Bruce (1977), that uterine artery ligation, in the pregnant guinea-pig at least, causes a reduction in maternal placental blood flow. Similar observations were made recently for the pregnant rat by Gilbert & Leturque (1982). Even though the relationship between placental size and maternal placental blood flow in the 49–51 days pregnant guinea-pig was linear it showed that as placental size fell there was a proportionately greater reduction in placental blood flow. Thus small placentas are associated with very low rates of maternal placental blood flow. This is likely to have considerable effect upon the balance between placental consumption and transport of nutrients with the small placenta needing proportionately more of the available substrate.

In view of this it is surprising that at the lower limit of this value variations of either placental blood flow or placental weights had a smaller effect upon fetal growth than normal. This is the converse of that found by Gilbert & Leturque (1982) where fetal weight and placental weight were related linearly over the whole range studied whilst fetal size fell sharply at low maternal placental blood flow rates. An explanation for the conservation of fetal weight despite very large reductions in placental weight and blood flow may be found in the changes in fetal body proportions

that occur with intra-uterine growth retardation. Reduced fetal size is associated with a proportionately greater fall in the size of the viscera and muscle tissues of the fetus that is more pronounced the greater the growth retardation (Hohenauer & Oh, 1969; Roux *et al.* 1970; Myers, Hill, Holt, Scott, Mellits & Cheek, 1971; Jones & Robinson, 1979; Lafeber *et al.* 1979; Robinson, Kingston, Jones & Thorburn, 1979). Should this lead not only to a reduced biosynthetic rate in the fetus but also to a marked reduction in basal metabolic rate that may be expected to result from falls in plasma insulin and thyroid hormone concentrations, the fetuses could to some extent counteract the presumed reduction in nutrient supply. A reduced oxygen consumption per unit weight of fetus has been observed in growth-retarded fetal sheep (J. E. Harding & C. T. Jones, unpublished observations).

In the growth-retarded fetal guinea-pigs the low plasma glucose concentration was associated with very low plasma insulin as has been observed also for the growth-retarded fetal rat (Girard *et al.* 1976) and sheep (Robinson *et al.* 1980). This implies a reduced fetal glucose consumption per unit mass. Thus it can be concluded that the effect upon fetal plasma glucose concentration of lowering maternal placental blood flow is indicative of a fall in glucose transport to the fetus. This is particularly apparent below flows of 5 ml./min where, if fetal glucose consumption is reduced also, the effect upon net glucose transport may be even greater than that indicated. An interpretation of this could be that the functional capacity of the placenta to transport glucose is reduced to a greater extent than the fall in placental size or in placental blood flow (Jones *et al.* 1981). However, the consumption of glucose by the placenta is high in relation to that by the fetus and in the sheep at least it could account normally for at least 50% of the total uteroplacental–fetal consumption (Meschia, Battaglia, Hay & Sparks, 1980; J. E. Harding & C. T. Jones, unpublished observations). Thus a reduction in placental blood flow relative to placental means could increase the proportion of glucose consumed compared to that transported by the placenta.

The weight of small fetal guinea-pigs is clearly much less sensitive to falls in the blood glucose concentration than are the normal fetuses. As discussed above, this could result in part from a reduced basal metabolic rate and altered fetal body proportion. Alternative explanations may be that the use of fuels other than glucose may increase relatively. Thus it is of note that in small fetuses the plasma concentration of amino acids and possibly lactate but not of fatty acids is higher than normal (Jones & Robinson, 1979; Lafeber *et al.* 1979; Robinson *et al.* 1979).

In summary, ligation of a uterine artery of the pregnant guinea-pig reduces maternal placental blood flow and fetal size more or less in proportion until flow is less than 50% of normal. Then the reduction in fetal size is less than would be expected despite a sharp fall in net glucose transport to the fetus. Under these conditions the net capacity for placental transport per unit weight of placenta is much reduced.

REFERENCES

ALEXANDER, G. (1964). Studies on the placenta of the sheep (*Ovis aries* L.): placental size. *J. Reprod. Fert.* **7**, 289–305.

BRUCE, N. W. (1977). The effect on fetal development and utero-placental blood flow of ligating uterine artery in the rat near term. *Teratology* **16**, 327–332.

BRUCE, N. W. & ABDUL-KARIM, R. (1973). Relationships between fetal weight, placental weight and maternal circulation in the rabbit at different stages of gestation. *J. Reprod. Fert.* **32**, 15–24.

DUNCAN, S. L. B. & LEWIS, B. V. (1969). Maternal placental and myometrial blood flow in the pregnant rabbit. *J. Physiol.* **202**, 471–481.

ELVIDGE, H. (1972). Production of dated pregnant guinea pigs without post-partum matings. *J. Inst. anim. Tech.* **23**, 111–117.

GILBERT, M. & LETURQUE, A. (1982). Fetal weight and its relationship to placental blood flow and placental weight in experimental intrauterine growth retardation in the rat. *J. devl. Physiol.* **4** (in the Press).

GIRARD, J. T., CHANEZ, C., KERVAN, A., TORDET-CARIDROIT, C. & ASSAN, R. (1976). Studies on experimental hypotrophy in the rat. III. Plasma insulin and glucagon. *Biologia Neonat.* **29**, 262–266.

GREENWOOD, F. C., HUNTER, W. M. & GLOVER, J. S. (1963). The preparation of ^{131}I-labelled human growth hormone of high specific radioactivity. *Biochem. J.* **89**, 114–123.

HOHENAUER, L. & OH, W. (1969). Body composition in experimental intrauterine growth retardation. *J. Nutr.* **99**, 23–26.

JONES, C. T. (1977). The development of some metabolic responses to hypoxia in the foetal sheep. *J. Physiol.* **265**, 743–762.

JONES, C. T., HARDING, J. E., ROBINSON, J. S., LAFEBER, H. N. & ROLPH, T. P. (1981). Aspects of the regulation of fetal growth. In *Advances in Animal and Comparative Physiology*, ed. PETHES, G. & FRENYO, V. L., pp. 53–60. Oxford: Pergamon Press.

JONES, C. T., LAFEBER, H. N., ROLPH, T. P. & FELLOWS, G. F. (1980). The timing of biochemical changes in development and their alteration by the growth rate of the fetus. In *Fetal Medicine*, ed. SALVADORI, B. & MERIALDI, A., pp. 86–109. Roma: Borla.

JONES, C. T. & ROBINSON, J. S. (1979). The influence of changes in the utero-placental circulation on the growth and development of the fetus. In *Maternal Effects in Development*, ed. NEWTH, D. R. & BALLS, M., pp. 395–409. Cambridge: Cambridge University Press.

KOLLE, L. A., MONNENS, L. A. H., TRIJBELS, J. M. F. & VEERKAMP, J. H. (1981). Carbohydrate metabolism in intrauterine growth retardation. In *Metabolic Adaptation to Extrauterine Life*, ed. DEMEYER, R., pp. 145–162. The Hague: Martinus Nijhoff Publications B.V.

KOLLE, L. A. K., MONNEUS, L. A. H., TRIJBELS, J. M. F., VEERKAMP, J. H. & JANSEEN, A. J. M. (1979). Experimental intrauterine growth retardation in the rat. Evaluation of the Wigglesworth model. *Early Human Development* **3**, 295–300

KULHANEK, J. R., MESCHIA, G., MAKOWSKI, E. L. & BATTAGLIA, F. C. (1974). Changes in DNA content and urea permeability of the sheep placenta. *Am. J. Physiol.* **226**, 1257–1263.

LAFEBER, H. N., JONES, C. T. & ROLPH, T. P. (1979). Some of the consequences of intrauterine growth retardation. In *Nutrition and Metabolism of the Fetus and Infant*, ed. VISSER, H. K. A., pp. 43–62. The Hague: Martinus Nijhoff Publishers B.V.

LEDUC, B. (1972). Maternal placental blood flow and gestational age in rabbits. *Am. J. Obstet. Gynec.* **122**, 374–378.

MCLAREN, A. (1965). Genetic and environmental effects on fetal and placental growth in mice. *J. Reprod. Fert.* **9**, 65–75.

MESCHIA, G., BATTAGLIA, F. C., HAY, W. W. & SPARKS, J. W. (1980). Utilisation of substrates by the ovine placenta *in vivo*. *Fedn Proc.* **39**, 245–249.

MYERS, R. E., HILL, D. E., HOLT, A. B., SCOTT, R. E., MELLITS, E. D. & CHEEK, D. B. (1971). Fetal growth retardation produced by experimental placental insufficiency in the rhesus monkey. I. Bodyweight, organ size. *Biologia Neonat.* **18**, 379–394.

ROBINSON, J. S., HART, I. C., KINGSTON, E. J., JONES, C. T. & THORBURN, G. D. (1980). Studies on the growth of fetal sheep. The effects of reduction of placental size on hormone concentration in fetal plasma. *J. Devl. Physiol.* **2**, 239–248.

ROBINSON, J. S., KINGSTON, E. J., JONES, C. T. & THORBURN, G. D. (1979). Studies on experimental growth retardation in sheep. The effect of removal of endometrial caruncles on fetal size and metabolism. *J. Devl. Physiol.* **1**, 379–398.

ROSENFELD, C. R., MORRISS, F. H., MAKOWSKI, E. L., MESCHIA, G. & BATTAGLIA, F. C. (1974). Circulatory changes in the reproductive tissues of ewes during pregnancy. *Gynecol. Invest.* **5**, 252–268.

ROUX, J. M., TORDET-CARIDROIT, C. & CHANEZ, C. (1970). Studies on experimental hypotrophy in the rat. I. Chemical composition of the total body and some organs in the rat foetus. *Biologia Neonat.* **15**, 342–347.

SASAKI, Y. & WAGNER, H. N. (1971) Measurement of the distribution of cardiac output in unanesthetized rats. *J. appl. Physiol.* **30**, 879–884.

SIMMONS, M. A., BATTAGLIA, F. C. & MESCHIA, G. (1979). Placental transfer of glucose. *J. Devl. Physiol.* **1**, 227–243.

SMITH, T. L. & HUTCHINS, M. (1980). Anaesthetic effects on dynamics of spontaneously hypertensive and Wistern Kyoto rats. *Am. J. Physiol.* **238**, H539–544.

STEGEMAN, J. H. J. (1974). Placental development in the sheep and its relation to fetal development. *Bijdr. Dierk.* **44**, 3–72.

THOMSON, A. M., BILLEWICZ, W. Z. & HYLTEN, F. E. (1969). The weight of the placenta in relation to birth weight. *Br. J. Obstet. Gynaec.* **76**, 865–872.

VAN DEN BERG, B. J. & YERUSHALMY, J. (1966). The relationship of the rate of intra-uterine growth in infants of low birth weight to mortality, morbidity and congenital anomalies. *J. Pediat.* **69**, 531–545.

WIGGLESWORTH, J. C. (1964). Experimental growth retardation in the fetal rat. *J. Path. Bact.* **88**, 1–13.

WOOTON, M., MCFADYEN, I. R. & COOPER, J. R. (1977). Measurment of placental blood flow in the pig and its relation to placental and fetal weight. *Biologia Neonat.* **31**, 333–339.