Fetal Growth Retardation

Animal Model: Uterine Vessel Ligation in the Pregnant Rat

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The infant who grows inadequately *in utero* has been recognized over the last 20 years under a number of different names, including intrauterine growth retardation, fetal malnutrition, dysmaturity, chronic fetal distress and small (or light)-for-dates. In the absence of those conditions known to impair fetal growth potential (certain infections—including rubella, trisomic syndromes, etc), fetal growth retardation may be seen in association with prolonged toxemia of pregnancy, or without obvious cause.[1] Fetal growth retardation may recur in successive pregnancies.[2] Infants with this condition are at increased risk from birth asphyxia and neonatal hypoglycemia, and there may be impairment in subsequent growth and development.[3] At necropsy, the features seen are similar to those of children suffering from malnutrition.[4]

Animal Model

The species used is the rat; strain differences in ease of production of the model have not been established. The female rat is anesthetised on the seventeenth day of pregnancy. The abdomen is shaved, and a midline laparotomy incision made with sterile precautions. The number of implantation sites in each uterine horn is checked, and one or more silk ligatures placed round the uterine vessels near the lower end of one horn. This ensures that the sole blood supply to the horn is that derived from the ovarian artery. The nonligated horn serves as a control. The abdominal incision is repaired in layers using standard surgical technic.

On killing the animal 4 to 5 days later, several growth-retarded fetuses may be found within the ligated horn, although some do not survive the

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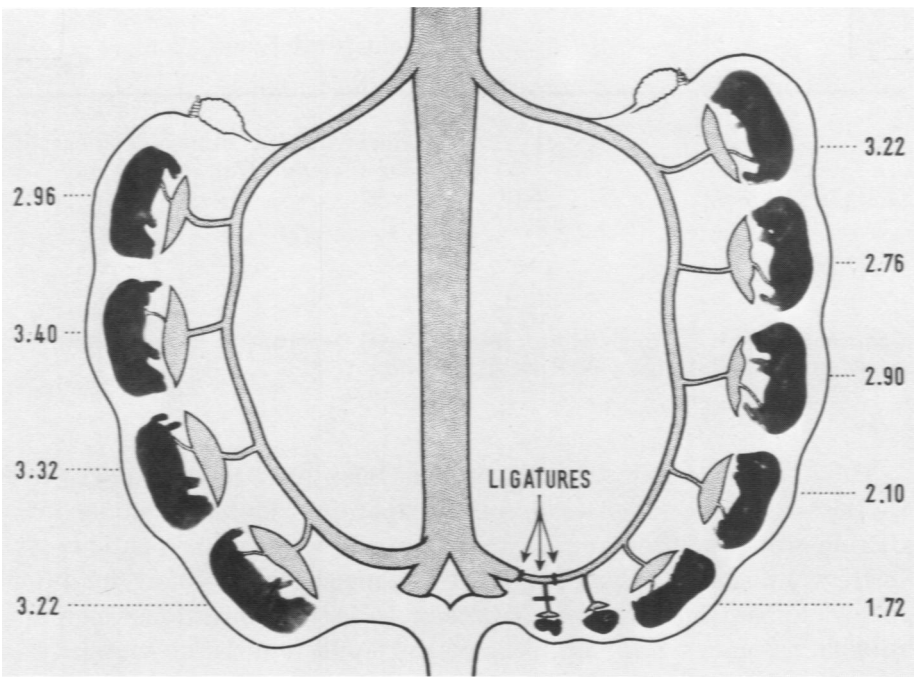

Fig 1—Diagram illustrating the uterine blood supply in the rat and a typical result of ligating the vessels to one uterine horn. Figures represent the weights in grams of individual fetuses 4 days after ligation. (Reproduced with permission from J Pathol Bacteriol.)

operation (Figure 1). As indicated in Figure 1, the most severely retarded fetuses are normally found in the sites nearest the ligature.

Most workers using the technic have killed the animals at term, but it is possible for them to be delivered and for the growth-retarded rats to be followed until adult life.[5]

The criterion for success in this model lies in the demonstration of a significant weight reduction in the fetuses in the experimental horn as compared to those in the control horn. Weight reduction may be as much as 60%, but 15 to 30% is more readily achieved.

Comparison With the Human Condition

In addition to the overall reduction in body size, the differential variation in organ weights is similar to that seen in man. The weight of the brain is maintained at the expense of internal organs such as the liver, lungs and kidneys,[6] as described in the human.[7] There is reduction in carbohydrate stores and there are low levels of serum proteins,[5] both well recognized in the human condition.[8]

The placenta, which in human fetal growth retardation is usually reduced in size,[9] shows no consistent pathologic findings, sometimes being small but often remaining of normal size. This may be due to the placenta having achieved near maximal growth by the seventeenth day of pregnancy when operation is performed.[10]

The main problem experienced with the model is to obtain a good yield of growth-retarded fetuses, since in some cases all the fetuses within the ligated horn die and in others there may be a great disparity in the number of implantation sites between the two horns, which then makes the experiment unreliable.

Usefulness of the Model

The model was originally designed to demonstrate the importance of the uterine blood supply as a controlling factor in fetal growth.[11] It provides a means of producing the fetal growth retardation picture in an internally controlled experiment, in that the normal-sized fetuses from the nonligated horn give a good control for other factors relating to fetal growth, such as maternal health and food intake and litter size effects.

The use of paired control and experimental fetuses from the same litter, as achieved with this model, obviates many of the statistical problems involved in work on litter-bearing animals and allows statistically significant results to be obtained from a small series of experiments.

Several groups of workers have found the model useful for studying biochemical changes associated with fetal growth retardation, including changes in body water, calcium and phosphate,[12] the development of hepatic enzymes associated with gluconeogenesis[13] and the changes in rate of DNA synthesis.[14]

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