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Factors influencing the outcome of ligating the uterine artery and vein in a guinea pig model of intrauterine growth retardation

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Introduction
Type II intrauterine growth retardation (IUGR), seen in the growth restricted human fetus, is characterised by asymmetric growth. In this condition body weight is affected more than length, and the brain and heart are developed at the expense of the abdominal organs (*Evans & Lin* 1984). A number of animal models of IUGR have been developed using the sheep and laboratory rodent, in which growth retardation is induced by a reduction of the placental blood supply, achieved by uterine artery ligation (*Wigglesworth*, 1964, *Lafeber* 1981, *Jansson et al.* 1986, *Carter & Detmer* 1990), placental embolization (*Creasy et al.* 1972, *Clapp et al.* 1984) or carunclectomy (*Alexander* 1964, *Robinson et al.* 1985, *Owens et al.* 1986).
Much recent research on IUGR has used the guinea pig model developed by *Lafeber* (1981). If the uterine artery is ligated early in pregnancy (30–32 days), some of the surviving fetuses have their growth retarded. An important feature of this model is the asymmetric growth of the fetus with the typical brain sparing pattern, resembling the type II IUGR human fetus.
The number of guinea pigs included in publications on IUGR is low when compared to the number allocated for study. A large part of the loss is due to unsuccessful outcome of the uterine artery ligation (*Lafeber* 1981). When combined with a complex sequence of surgical procedures, fetal/experimental loss is compounded. For example, *Jansson & Persson* (1990) ligated the uterine artery in 135 animals but only 14 % ended as successful experiments.
We have addressed the issue of whether the number of animals used can be reduced by taking account of factors that may influence the outcome of uterine artery ligation. Factors considered were day of pregnancy at ligation, the ligation technique and maternal weight on the day of ligation.

Materials and methods
Animals: Guinea pigs of outbred stock (Ssc:AL), were housed under controlled environmental conditions (21 ± 1°C, 55 ± 5 % relative humidity and a 12 hour light/dark cycle) and given free access to a guinea pig maintenance diet (Altromin 3120) and tap water. Selenium/vitamin E and vitamin C were added to the tap water each time the water bottle was changed. The animals were kept in Macrolon®-IV cages on beechwood shavings that were changed three times a week, at which time they also were given autoclaved meadow hay.
The female guinea pig usually has a regular estrous cycle with a mean interval between ovulations of 16 days at 10–12 weeks of age, at which time body weight is about 500 grams. Two females and one male were housed together. Pregnancy was determined by daily inspection of the vaginal membrane as described by *Elvidge* (1972). Day 0 of pregnancy was defined as the first day on which the vaginal membrane was fully open. Mating usually occurs on the following day (*Reed & Hounslow* 1971).

Surgical technique. At day 29–33 of pregnancy the guinea pigs were anaesthetized using xylazine 4 mg/kg bw and ketamine 60 mg/kg bw (Rompun® and Ketalar®). Xylazine was administered either sc or im and ketamine given either ip or sc. In our experience subcutaneous administration of these drugs is less traumatic for the animal. Atropine 0.05 mg/animal was used as premedication to reduce airway secretion. The skin of the lower abdomen was clipped, treated with 70 % ethanol and wrapped with plastic film. If necessary the skin was infiltrated with 1 % lidocaine (Xylocain®). Access to the lower abdomen was gained though a 2 cm midline incision caudal to the umbilicus. The mesometrial fat pad of one uterine horn was exposed, lifted and turned and the uterine artery or the uterine artery and vein embedded in it were ligated from the dorsal side with surgical silk at the level of the cervix (see fig. 1). This could be done without disturbing the opposite horn. Finally 1–2 ml of sterile physiological saline solution was instilled before closing the abdominal wall in 2 layers (fascia and skin) with continuous stitching. Aseptical technique was used throughout the operation, which lasted 10–15 minutes. During the postoperative period the animals were kept under an infrared lamp. The guinea pigs were fully awake and could be returned to their cages after 2–3 hours.

Methods: The data used in this study were collected from 3 periods of research in fetal physiology (*Carter & Detmer* 1990, *Detmer et al.* 1991 and in preparation). A total number of 235 pregnant guinea pigs was used. We included guinea pigs with at least one normally grown fetus in the control horn and/or a fetus showing retarded growth in the horn on the ligated side. A growth retarded fetus was defined as a fetus from the ligated side with a brain/liver weight ratio of $\geq$ 0.85. The liver was weighed with the gall bladder intact, the brain was cut loose from the spinal cord, so that it included the medulla oblongata. Natural runts were not included (in our animals they were not common). For bilateral pregnancies, the mean weight of fetuses from the control horn was used as a reference for fetuses from the ligated horn. For unilateral pregnancies, the mean weight of the control fetuses for that day of pregnancy was used as a reference. We made note of fetuses that were wholly or partially resorbed and distinguished between these and fetuses that had continued to grow after vessel ligation yet died before the final examination.

On the day of ligation the following were noted: maternal weight, position of the ligature (right or left, artery + vein or just artery), date of ligation and day of pregnancy. Additional information was registered on the day of the subsequent experiment: day of pregnancy, maternal weight, fetal and placental weights, fetal location in the uterus, and brain and liver weights of all fetuses on the ligated side. The site of the ligature, and its success or failure, were also checked.

Statistics: For statistical calculations the normal test for comparing two proportions or the Student's t-test were used (*Kirkwood* 1988). The outcome of ligating on different days was tested using Fisher's exact test. Significance was accepted at the 5 % level ($p < 0.05$).

Results

The 235 pregnant animals included 187 bilateral and 48 unilateral pregnancies. The

Table 1. Overall results of uterine artery or uterine artery and vein ligation at day 29–33 of pregnancy. The terminal experiment was performed on day 60–64.

Fetal outcome per experiment	Number of animals	%
No surviving fetuses	80	34
No IUGR fetuses	56	24
One/several IUGR fetuses	99	42
Total number of animals	235	100

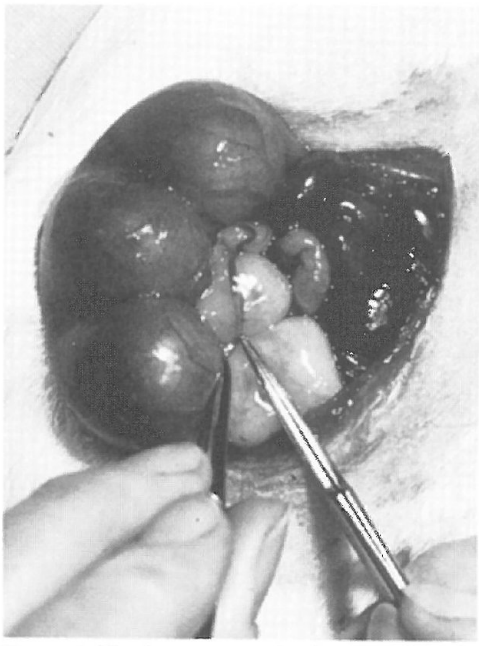

Figure 1. Uterine artery and vein supplying the right uterine horn of a guinea pig of the 30th day of pregnancy. To provide intrauterine growth retardation, the artery, with or without the accompanying vein, was ligated at the level indicated by the forceps. The procedure was performed through a small incision in the abdominal wall and did not require exteriorization of the uterus.

vessels supplying the left horn were ligated in 120 of the bilaterally pregnant animals. Twenty-three of the unilateral pregnancies were in the left horn. The overall results of ligating the uterine artery or the uterine artery and vein are presented in table 1. In 42 % of all guinea pigs used, a growth retarded fetus was available for experiment.

There was a significant difference ($p < 0.002$, normal test) in the outcome of ligation (irrespective of ligation technique) between unilateral and bilateral pregnancies. The 48 ligations in unilateral pregnancies gave 21 % with IUGR fetuses compared to 48 % for bilateral pregnancies. The difference between ligating just the artery or both artery and vein was significant ($p < 0.01$, normal test) in bilateral pregnancies but not in unilateral pregnancies. However, the number of unilateral pregnancies was small. In fig. 2 the influence of the ligation technique on the outcome of the experiment is presented graphically. The artery and vein were ligated in a total of 142 animals pregnant in both horns; in 45 % of these experiments, all fetuses on the ligated side were resorbed, whereas in 42 % at least one IUGR fetus was available for experiment. When just the artery was ligated, all fetuses

Table 2. Fetal outcome following ligation of the uterine artery alone or together with the accompanying vein in bilateral and unilateral pregnancies. Guinea pigs were operated on day 29–33 and the terminal experiment performed on day 60–64.

Fetal outcome per experiment	Bilateral pregnancies	Unilateral pregnancies	Total
A. Ligation of uterine artery alone			
All dead	3 (7 %)	0 (0 %)	3 (5 %)
No IUGR fetuses	13 (29 %)	8 (62 %)	21 (36 %)
One/several IUGR fetuses	29 (64 %)	5 (38 %)	34 (59 %)
Total	45 (100 %)	13 (100 %)	58 (100 %)
B. Ligation of uterine artery and vein			
All dead	63 (45 %)	14 (40 %)	77 (43 %)
No IUGR fetuses	19 (13 %)	16 (46 %)	35 (20 %)
One/several IUGR fetuses	60 (42 %)	5 (14 %)	65 (37 %)
Total	142 (100 %)	35 (100 %)	177 (100 %)

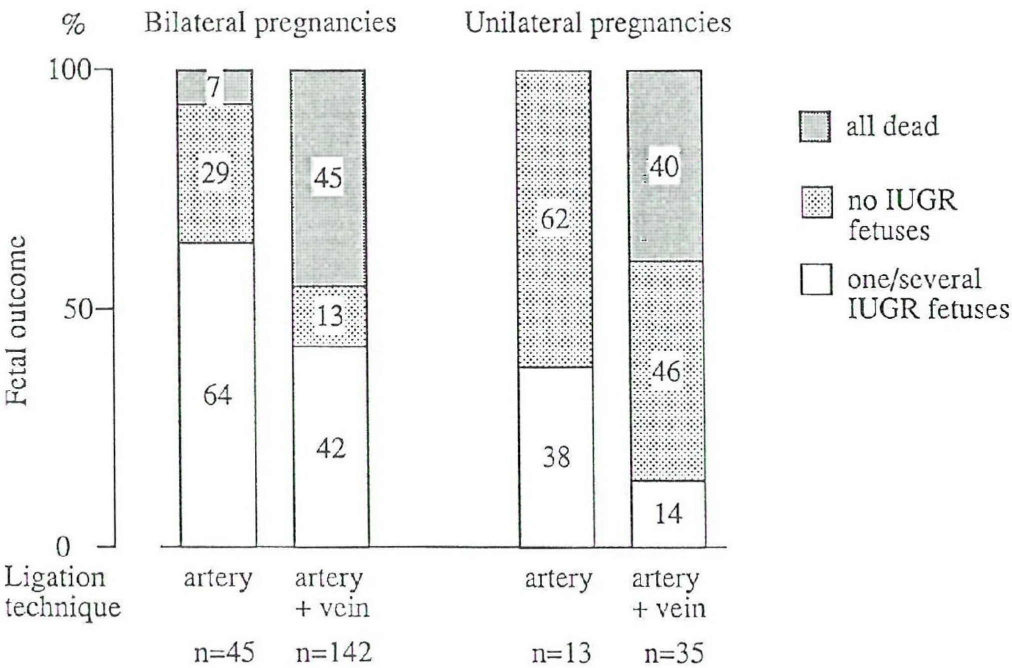

Figure 2. Influence of the ligation technique on fetal outcome following uterine artery ligation analyzed by experiment in unilateral and bilateral pregnancies. Guinea pigs were operated on day 29–33 and the terminal experiment performed on day 60–64.

on the ligated side were resorbed or dead in 7 % of the guinea pigs whilst 64 % had at least one IUGR fetus. For unilateral pregnancies, ligating the artery alone gave no experiment in which all the fetuses had died and 38 % of the animals had an IUGR fetus. Ligating both artery and vein in unilateral pregnancies gave 40 % where all the fetuses died and 14 % with IUGR fetuses.

Outcome by maternal weight is shown in table 3. There was a significant ($p < 0.05$, normal test) difference between animals weighing less than 600 grams and animals weighing more than 600 grams in the proportion of animals with at least one IUGR fetus.

We also analyzed our data for seasonal differences. The percentage of IUGR fetuses

Table 3. Fetal outcome following uterine artery or uterine artery and vein ligation in guinea pigs weighing more or less than 600 grams on the day of ligation. Guinea pigs were operated on day 29–33 of pregnancy and the terminal experiment performed on day 60–64.

Fetal outcome per experiment	Maternal weight in grams		
	< 600 grams	≥ 600 grams	Total
All dead	13 (47 %)	67 (32 %)	80
No IUGR fetuses	9 (32 %)	47 (23 %)	56
One/several IUGR fetuses	6 (21 %)	93 (45 %)	99
Total	28 (100 %)	207 (100 %)	235

Table 4. Fetal outcome following uterine artery or uterine artery and vein ligation analyzed by day of ligation. Guinea pigs were operated on day 29–33 and the terminal experiment performed on day 60–64.

Fetal outcome per experiment	Day of ligation					
	29	30	31	32	33	Total
All dead	7 (44 %)	19 (27 %)	24 (37 %)	16 (50 %)	0	66
No IUGR fetuses	3 (19 %)	11 (16 %)	14 (22 %)	4 (12 %)	0	32
One/several IUGR fetuses	6 (37 %)	40 (57 %)	26 (41 %)	12 (38 %)	5 (100 %)	89
Total	16 (100 %)	70 (100 %)	64 (100 %)	32 (100 %)	5 (100 %)	187

With Fisher's exact test the proportions of IUGR fetuses on the different days of ligation were each compared to day 30. The differences were not significant.

among the survivors was 60 % (32/54) in Spring and 85 % (57/67) during the Autumn. The difference was significant ($p < 0.005$, normal test).

The statistical analysis of outcome by day of ligation for bilateral pregnancies (table 4) revealed no significant difference (Fischer's exact test) in the number of animals with at least one IUGR fetus on days 29 or days 31–33, when each day was compared with day 30.

The fetal weight/placental weight ratios were calculated for all surviving fetuses on days 60 and 62. No significant difference in this ratio was found between fetuses in the control horns and those on the ligated side, between control fetuses and those defined as IUGR, or between IUGR fetuses and fetuses from the ligated side that did not satisfy our definition of IUGR (Student's t-test).

Discussion

Definitions of IUGR vary greatly. In pediatric medicine, 2 SD below normal weight or less than the 10th percentile for gestational weight at birth is often used (*Lin & Evans* 1984). Not all children classified as small for gestational age (SGA) are growth retarded (*Vilbergsson* 1991); some of the SGA babies are small but well proportioned and thus not included in type II IUGR. In this guinea pig model of IUGR we define a growth retarded fetus as one on the ligated side with a brain/liver weight ratio ≥ 0.85. *Lafeber* (1981) reported growth retardation, defined as at least one live fetus with < 60 % of the normal body weight, in 30 % of the 372 guinea pigs that were operated. If we had used *Lafeber*'s (1981) definition of IUGR we would have classified 28 % as successful, whereas with one of *Jansson*'s (1990) criteria (< 80 % of mean bw) 48 % would have been usable. The easiest way to achieve higher numbers of IUGR pregnancies is to change the definition of IUGR. However, we feel our definition of IUGR is optimal since it ensures that only growth retarded fetuses with asymmetric growth are included in a study. Human type II IUGR is typified by asymmetric growth and therefore we find it of questionable value to include fetuses lacking the typical brain sparing feature.

In our experience guinea pig fetuses close to the cervix are more prone to resorption than fetuses implanted at the tubal end. If there were several fetuses on the ligated side, the largest one was usually at the ovarian end of the uterine horn (36 of 42 bilateral pregnancies with > 1 surviving fetus, 86 %). In *Wigglesworth*'s (1964) rat experiments, fetuses close to the ligature died, and those at the ovarian end were largely unaffected, whereas the fetuses in the midsection of the horn exhibited various degrees of IUGR. Thus, fetuses implanted at the ovarian end of the ligated horn have a greater chance of surviving the ligation.

The site of implantation is an important factor, but not one that the experimentator can control. This applies also to unilateral pregnancies. The discouraging results in outcome of uterine artery and vein ligation in unilaterally pregnant animals are particularly noteworthy. Ligating the artery alone in unilaterally pregnant animals yielded a higher number of survivors, but many of them were too large to satisfy our definition of IUGR. To save animals it is better to identify unilateral pregnancies (this is easily done by palpation from the outside before the ligation procedure), and use them as sham operated controls or allocate them to a parallel project that requires only normally grown fetuses.

Each horn of the guinea pig uterus is supplied by a uterine and an ovarian artery (*Egund & Carter* 1974). Total blood flow to the uterus increases 15–20 fold during pregnancy in the guinea pig (*Hart et al.* 1985), and if the supply from the ovarian artery can be increased to an even greater extent, this will partly compensate for ligation of the uterine artery. We saw a significant difference in fetal outcome with respect to ligation technique, in that all fetuses were resorbed or dead in 43 % of experiments where both artery and vein were ligated compared to 5 % when only the artery was ligated (unilateral and bilateral pregnancies pooled). This suggests that, in the acute phase immediately following uterine artery ligation, the ovarian artery has a better chance of maintaining blood flow when the venous drainage is left undisturbed. Once the new pattern of circulation has been established, the presence or absence of a uterine vein makes no difference to the incidence of IUGR fetuses. This interpretation is in accordance with our observation that the proportion of fetuses that die later in gestation was similar in both groups (7–8 %).

It should be noted that many fetuses on the ligated side (especially in unilateral pregnancies) were too large to satisfy our definition of IUGR after ligation of the uterine artery alone. Moreover, it is often rather difficult to ligate just the artery without disturbing the vein, since the artery is in close apposition to, and interwoven with, the uterine vein. Therefore, we recommend ligating the artery alone when this is possible without traumatizing the fat pad, otherwise both vessels should be ligated.

The analysis by day of ligation does not give any reason to change the standard procedure of performing the uterine artery ligation on day 30 of gestation. It would, however, be interesting to see a follow-up study on the outcome of uterine artery ligation later than day 32 of gestation, since the 5 animals operated on day 33 of pregnancy all had a growth retarded fetus.

The mother's weight at the time of mating is important. There was a significant difference in outcome between guinea pigs weighing $<$ 600 grams on the day of ligation and those that had attained a weight $>$ 600 grams. We conclude that mating should not start until the female guinea pig weighs $>$ 500 grams. The male guinea pig reaches sexual maturity later than the female and should be correspondingly larger, about 600 grams.

The unaltered fetal weight/placental weight ratio for the IUGR fetuses in this and previous studies (*Jansson & Persson* 1990) is in accordance with data for the growth retarded human infant at the time of delivery (*Nylund et al.* 1983).

Acknowledgements

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Summary

In a retrospective study the outcome of uterine artery or uterine artery and vein ligation in 235 pregnant guinea pigs was reported. The aim of the study was to reduce the number of animals used in studies of IUGR, by identifying factors influencing the outcome of uterine artery ligation that could easily be changed. Differences in outcome by ligation technique, day of ligation and maternal weight on day of ligation were analyzed. Ligating only the artery gave better results in bilateral pregnancies, and animals with bilateral pregnancies had IUGR fetuses more often than unilaterally

pregnant animals. No significant difference in number of IUGR fetuses per experimental animal between different days of ligation (29–33) was seen. Better results were obtained with animals weighing > 600 grams at the time of ligation.

Sammanfattning

Utfallet av underbindning av arteria uterina på 235 dräktiga marsvin analyserades i en retrospektiv undersökning. Syftet med undersökningen var att minska antalet djur som används i forskning om tillväxthämning. Detta genom att identifiera ändringsbara faktorer som påverkade utfallet. Skillnader mellan ligeringsteknik och tidpunkt för ligering liksom skillnader av moderns vikt på ligeringsdagen undersöktes. Att ligera endast artären gav bättre resultat vid dubbelsidiga dräktigheter. Djur dräktiga i båda horn hade IUGR foster oftare än enkelsidigt dräktiga djur. Ingen signifikant skillnad i antal erhållna IUGR foster vid ligering på olika dräktighetsdagar (29–33) sågs. Bättre resultat erhölls med djur som vägde > 600 gram vid tidpunkten för ligeringen.

Yhteenveto / K. Pelkonen

Tässä retrospektiivisessä työssä selvitettiin kohtuvaltimon ja toisaalta sekä kohtuvaltimon että kohtulaskimon sitomisen vaikutuksia 235:llä kantavalla marsulla. Tutkimuksen tarkoituksena oli vähentää kasvun vähentymisen tutkimiseen käytettävien eläinten määrää tunnistamalla ne valtimositomisen vaikutuksiin liittyvät tekijät, joihin voidaan helposti vaikuttaa. Työssä selvitettiin sitomistekniikan, sitomisajankohdan ja emon painon aiheuttamia eroja. Molemminpuolisessa tiinehtymisessä valtimonsitominen antoi parhaat tulokset ja näissä eläimissä poikasissa havaittiin kasvun hidasturmista useammin kuin toispuoleisesti tiineissä eläimissä. Sitomispäivä ei vaikuttanut kasvussa hidastuneiden poikasten määrään välillä 29–33 päivää. Parempia tulkosia saatiin eläimissä, joiden paino oli sitomishetkellä yli 600 g.

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Eigil Frank, Levnedsmiddelstyrelsen, Søborg: "Vejeprogram dyrvej 90".

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