Effects of unilateral uterine artery ligation on skin development

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Summary

Background: It has been previously demonstrated that intrauterine growth retardation (IUGR) due to vascular insufficiency in humans results in newborn infants with marked loss of subcutaneous fat and decreased content of differentiation-specific epidermal structural proteins.

Objective: In this study, the teratogenic effects of impaired maternal blood flow were investigated histologically on rat skin.

Materials & Methods: Twenty Spraque-Dawley female rats were separated into two groups (n=10), a control (sham-operated) and an experimental group. The experimental group of fetal rats were subjected to IUGR by unilateral ligation of the maternal uterine artery on the 18th day of pregnancy. The maternal rats were subjected to cesarean hysterectomy on the 21st day of pregnancy and a skin biopsy was taken from the respective litters of both groups.

Results: In histopathological examination, normal epidermis and dermis were observed in the control group of litters and littermate rats from the opposite uterine horn (non-ligated side). A statistically significant reduced body weight and height were noted in the ligated side of the litters.

Conclusion: Our findings give further evidence to the concept that normal maternal blood flow is essential for fetal growth and decreased maternal blood flow may create an impairment in skin development.

Key words: Artery ligation; Newborn rat skin; Uterine artery.

Introduction

Fetal growth can be influenced by a number of important genetic, environmental, and maternal factors. These include a variety of congenital malformations and chromosomal disorders, environmental toxins such as cigarette smoking and alcohol, and maternal medical conditions which can restrict the nutrient supply to the fetus [1].

Impaired maternal blood flow is one of the major causes of intrauterine growth retardation which may lead to perinatal morbidity and mortality in humans. In animal models, impaired maternal blood flow has been accomplished by unilateral ligation of the uterine artery. Major developmental abnormalities of internal organs have been reported following unilateral ligation of the uterine artery. However, the teratogenic effects of impaired maternal blood flow on skin development have not been well documented. In this present study, the teratogenic effects of impaired maternal blood flow were investigated histologically on rat skin.

Materials and Methods

Twenty Spraque-Dawley female rats were separated into two groups (n=10), a control (sham-operated) and an experimental group. The experimental group of rats were subjected to unilateral ligation of the uterine artery in order to create decreased maternal blood flow on the 18th day of pregnancy. The pregnant rats were subjected to cesarean hysterectomy on the 21st day of pregnancy. After cesarean hysterectomy, the respective litters were weighed and their lengths were measured and a skin biopsy was taken in both groups of litters. Tissue samples were fixed in a solution of 10% formaldehyde. The tissues were then embedded in paraffin wax, serial sectioned and stained with hematoxylin-eosin for evaluation using a light microscope. Histopathological assessments were made on all groups.

Results

In the experimental group of dam rats, dead fetuses were noticed in the ligated side of the uterus during cesarean hysterectomy (Table 1). A statistically significant reduced body weight and length were noted in the fetuses in the experimental group of litters (Table 2).

The weights were analysed by ANOVA procedures followed by a multiple comparison procedure based on the Tukey-HSD method. The results of the ANOVA were significant ($p<0.0001$) and the multiple comparison procedure indicated that the following treatments were significantly different at $p<0.05$:

– Control group *versus* experimental group of non-ligated side;

– Control group *versus* experimental group of ligated side;

– Experimental group of non-ligated side *versus* experimental group of ligated side.

The lengths were analysed by ANOVA procedures followed by a multiple comparison procedure based on the Tukey-HSD method. The results of the ANOVA were significant ($p<0.0001$) and the multiple comparison procedure indicated that the following treatments were different at $p<0.05$:

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Table 1. — *The number of fetus deaths in the control and experimental group of dam rats.*

Indices (Dam rats)	*Number of dead fetuses* Control group	*Number of dead fetuses* Experimental group (Non-ligated side)	*Number of dead fetuses* Experimental group (Ligated side)
1	(–)	(–)	2
2	(–)	(–)	3
3	(–)	(–)	2
4	(–)	(–)	2
5	(–)	(–)	3
6	(–)	(–)	3
7	(–)	(–)	1
8	(–)	(–)	1
9	(–)	(–)	2
10	(–)	(–)	1
Total	(–)	(–)	20

Table 2. — *Mean weight and length of the litters in the control and experimental group.*

Indices (Dam rats)	*Mean weight/length* Control group	*Mean weight/length* Experimental group (Non-ligated side)	*Mean weight/length* Experimental group (Ligated side)
1	6.55 g/6.50 cm	6.15 g/6.50 cm	4.75 g/5.50 cm
2	6.30 g/7.00 cm	6.00 g/6.00 cm	5.25 g/5.75 cm
3	6.50 g/7.25 cm	6.35 g/6.75 cm	4.65 g/5.00 cm
4	6.75 g/7.50 cm	6.15 g/6.25 cm	4.95 g/5.25 cm
5	6.05 g/8.00 cm	6.05 g/7.00 cm	4.85 g/5.50 cm
6	6.65 g/7.75 cm	6.00 g/6.50 cm	5.20 g/5.75 cm
7	6.40 g/7.00 cm	5.65 g/6.25 cm	4.65 g/5.25 cm
8	6.60 g/8.00 cm	6.25 g/6.50 cm	4.60 g/5.00 cm
9	6.40 g/6.00 cm	6.05 g/6.00 cm	4.75 g/5.75 cm
10	6.50 g/7.50 cm	6.15 g/6.25 cm	4.85 g/5.25 cm
Mean	6.47 g/7.25 cm	6.08 g/6.40 cm	4.85 g/5.40 cm
Standard Deviation	0.20/0.65	0.19/0.32	0.22/0.29

– Control group *versus* experimental group of non-ligated side;

– Control group *versus* experimental group of ligated side;

– Experimental group of non-ligated side *versus* experimental group of ligated side.

At histopathological examination, normal epidermis and dermis were observed in the control and non-ligated side of the experimental group of litters (Figures 1, 2, 3). However, atrophic epidermis with loss of rete ridges was striking in the ligated side of the experimental group of litters (Figures 4, 5).

Discussion

Uteroplacental insufficiency alters the anabolic metabolism of the fetus, resulting in intrauterine growth retardation (IUGR) which is a common complication of pregnancy. The metabolic and physiologic factors that cause IUGR have long standing consequences after birth.

Major developmental abnormalities of internal organs have been reported following unilateral ligation of the uterine artery [2-7]. IUGR due to vascular insufficiency in humans results in newborn infants with marked loss of subcutaneous fat and dysmature appearance of the epidermis. Hoath *et al.* [8] demonstrated that fetal rats subjected to intrauterine growth retardation exhibit a thinner stratum corneum and decreased content of differentiation-specific epidermal structural proteins (keratins,

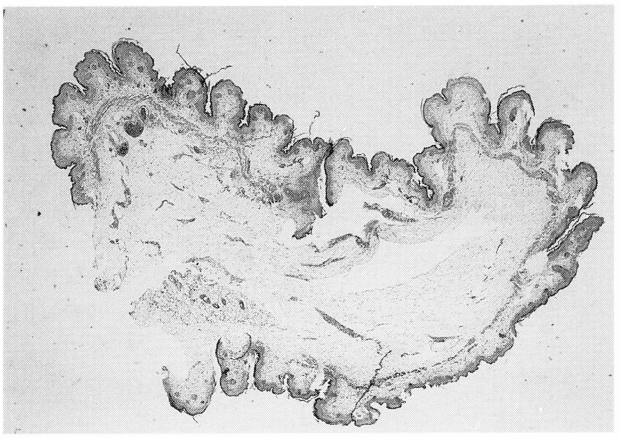

Figure 1. — Normal epidermis and dermis in the control group of litters (H&E, original magnification x 16).

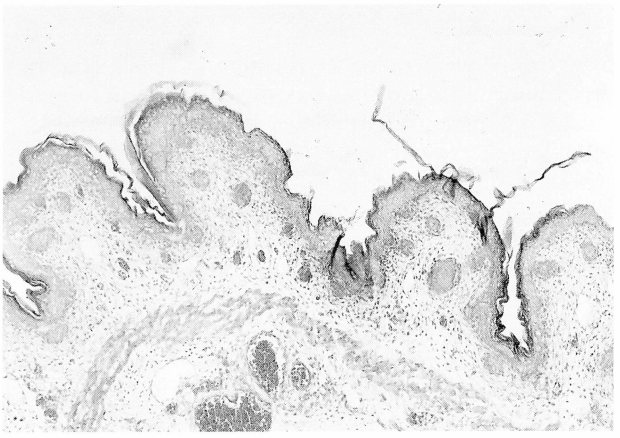

Figure 2. — Normal epidermis and dermis in the control group of litters (H&E, original magnification x 41).

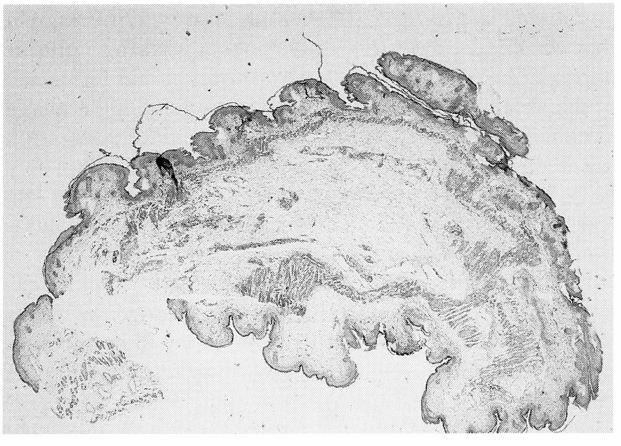

Figure 3. — Normal epidermis and dermis in the non-ligated side of the experimental group of litters (H&E, original magnification x 16).

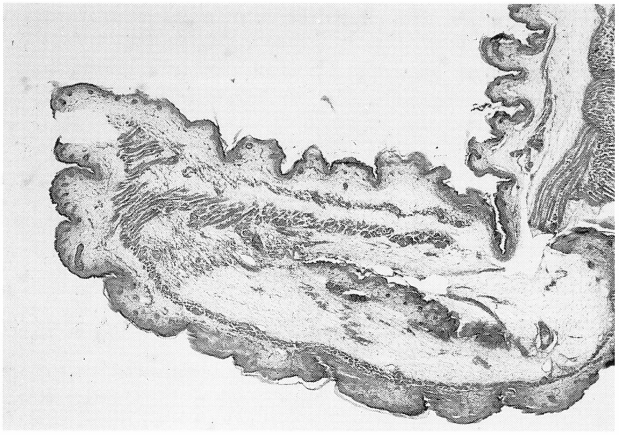

Figure 4. — Prominent atrophic epidermis with loss of rete ridges in the ligated side of the experimental group of litters (H&E, original magnification x 16).

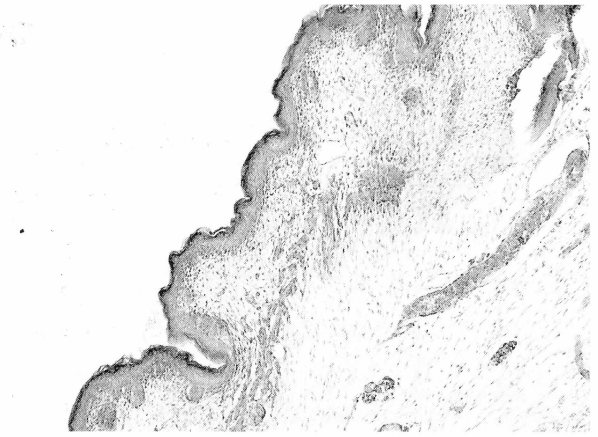

Figure 5. — Prominent atrophic epidermis with loss of rete ridges in the ligated side of the experimental group of litters (H&E, original magnification x 41).

filaggrin). However, barrier function in IUGR fetal rats was found to be normal despite significant somatic growth retardation and a thinner stratum corneum [9].

Epidermal growth factor (EGF) is a mitogenic polypeptide hormone which plays a role in a variety of biological actions including promotion of epidermal development, wound healing, activation of various transport systems and changes in cellular metabolism. Lawrence *et al.* [1] demonstrated an increased synthesis of EGF receptors in IUGR fetal rats. They concluded that increased synthesis of EGF receptors would be a response to decreased maternal blood flow in order to enhance not only skin maturation but also nutrient uptake.

In general, the direct effect of impaired blood supply on differentiating epithelia has not been fully understood. In humans, pulmonary maturation has been reported to be both accelerated [10] and retarded [11] relative to the gestational age of the IUGR infant. However, it is known that the fetal epidermis undergoes a striking cellular hyperplasia associated with keratinization and formation of the stratum corneum [12]. In human fetal epidermis, a similar pattern of rapid cell division and keratinization has been shown during the final trimester of pregnancy [13]. Therefore, it is important to speculate that the late stages of pregnancy are a critical period for skin maturation in humans and animals.

In summary, we observed histologically atrophic epidermis with loss of rete ridges as the teratogenic effects of unilateral uterine artery ligation on rat skin development. Our findings and those previously reported [8] give further evidence to the concept that normal maternal blood flow is essential for fetal growth and decreased maternal blood flow may create an impairment of skin development.

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