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Review

Environmental factors affecting pregnancy: Endocrine disrupters, nutrients and metabolic pathways

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ABSTRACT

Uterine adenogenesis, a unique post-natal event in mammals, is vulnerable to endocrine disruption by estrogens and progestins resulting in infertility or reduced prolificacy. The absence of uterine glands results in insufficient transport of nutrients into the uterine lumen to support conceptus development. Arginine, a component of histotroph, is substrate for production of nitric oxide, polyamines and agmatine and, with secreted phosphoprotein 1, it affects cytoskeletal organization of trophectoderm. Arginine is critical for development of the conceptus, pregnancy recognition signaling, implantation and placentation. Conceptuses of ungulates and cetaceans convert glucose to fructose which is metabolized via multiple pathways to support growth and development. However, high fructose corn syrup in soft drinks and foods may increase risks for metabolic disorders and increase insulin resistance in adults. Understanding endocrine disrupters and dietary substances, and novel pathways for nutrient metabolism during pregnancy can improve survival and growth, and prevent chronic metabolic diseases in offspring.

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1. Introduction

Key events affecting the ability of mammals to reproduce begin in utero with differentiation of the gonads and male and female reproductive systems. However, full differentiation of the female reproductive system is a unique postnatal event in mammals that

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is vulnerable to endocrine disrupters such as environmental estrogens and progestins that render the uterus nonfunctional (see Bartol et al., 1988). Endocrine disrupters of uterine adenogenesis have downstream effect to render females subfertile or infertile. This review focuses on endocrine disrupters that prevent development of uterine glands to adversely affect fertility, as well as the importance of the uterus in providing mechanisms for transport of nutrients from the environment into the uterine lumen where they are used via various metabolic pathways to support growth, differentiation and development of the conceptus (embryo/fetus and associated membranes).

2. Endocrine disrupters of uterine adenogenesis and fertility

Uterine adenogenesis, the morphological differentiation and development of the uterus, particularly uterine glands, is a unique postnatal event in mammals (see Fig. 1). Adenogenesis is vulnerable to adverse effects of endocrine disrupters in the environment such as progestins and estrogens as reviewed previously (Gray et al., 2001a; Spencer and Bazer, 2004a). Sheep and other ruminant species exposed to forages that contain estrogenic activity experience hyperplasia of endometrial glands, dystocia, prolapse of the uterus, and infertility (Adams, 1995; Lindner, 1976). Experimentally, chronic

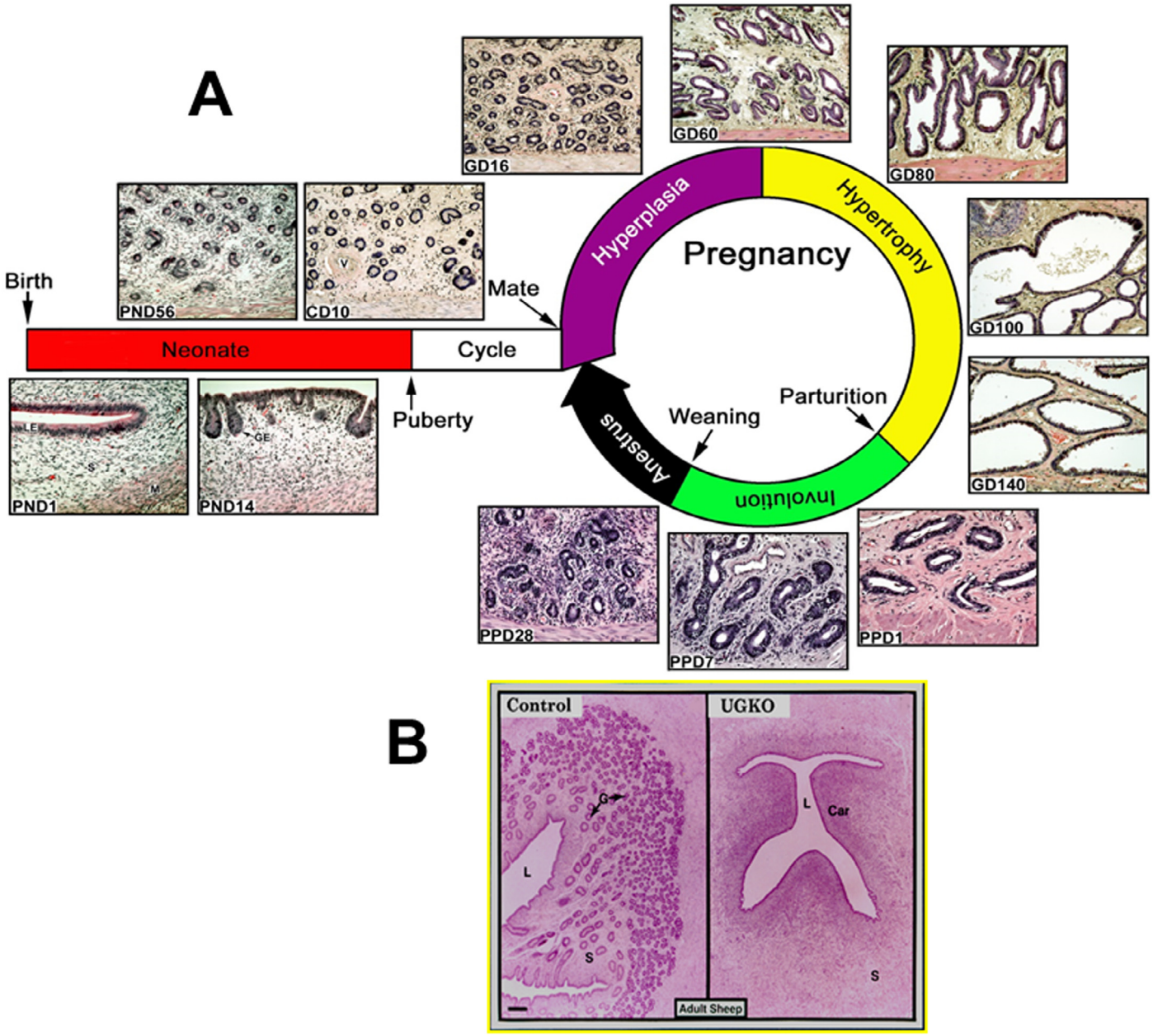

Fig. 1. (A) The neonatal ovine uterus on postnatal day (PND) 1 does not have uterine glands, but these develop through buding from the lumenal epithelium and then invasion at glands lined with glandular epithelium that progress through the stroma toward the myometrium while differentiating through branching morphogenesis to fully developed uterine glands by PND56. The glands are shown from Day 10 of the estrous cycle (CD10) and then undergoing hyperplasia between gestational days (GD) 16 and 60 and they hypertrophy as the uterine glands fill with hystotroph between GD 80 and 140 of a 147 day period of gestation. Following parturition, the uterus undergoes rapid involution between post-partum (PP) Days 1–28. (B) The uterus of a normal control adult ewe contains many uterine glands, but a ewe treated with a progestin from PND1-56 fails to develop uterine glands and these ewes do not exhibit normal estrous cycles and they are infertile (see Spencer and Bazer, 2004a).