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Chronic maternal inflammation during late gestation impairs subsequent β-cell function but not islet growth in fetal sheep

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ABSTRACT: Intrauterine growth restriction (IUGR) greatly increases perinatal mortality and morbidity rates, and leads to much greater risk for metabolic complications later in life. One such complication is the development of glucose intolerance or diabetes, which typically develops concurrently with abhorrent patterns of insulin secretions due to diminished β-cell mass and impaired function as well as an overall reduction in pancreatic endocrine tissue. The mechanisms by which IUGR causes problems with health and function of the pancreatic islets are not well understood. Therefore, our goal for this study was to determine how materno-fetal inflammation (MI) affects β-cell growth and function. To do this, we compared the average islet areas, plasma insulin concentrations, and blood glucose concentrations between MI-IUGR fetal lambs (n = 7) and control fetal lambs (n = 7). Pregnant ewes were injected with saline (controls) or 0.1-μg/kg bacterial lipopolysaccharide (LPS) every 3 d from days 100 to 115 of gestation (term = 150 d). Throughout late gestation, arterial blood of the fetus was periodically drawn and analyzed for plasma insulin (ELISA) and blood glucose (ABL90 FLEX) levels. On day 125 of gestation, ewes were euthanized and fetal pancreas was extracted. Sections of the fetal pancreas were then fixed in 4% paraformaldehyde, sectioned (cryostat) at a thickness of 8 μm, stained for insulin-positive area, and imaged on 20x magnification for analysis of average islet area. Between MI-IUGR and control fetuses, there were no differences in average islet areas (1675 ± 286 and 1678 ± 287 μm^2, respectively), which indicates that MI did not impair growth and physical development of fetal islets. In addition, blood glucose was similar in all fetuses. However, results showed less ($P \leq 0.05$) plasma insulin concentration in MI-IUGR fetuses (0.39 ± 0.07 ng/mL) than in controls (0.70 ± 0.09 ng/mL). This indicates impaired β-cell functional capacity in MI-IUGR fetuses despite normal growth, which is quantified by a tendency (P = 0.08) for strong positive correlation (r = 0.91) between plasma insulin and islet area in control fetuses but an absence of correlation in MI-IUGR fetuses. From this study, we can conclude that MI-IUGR has no effect on the growth and physical development of β cells; however, it does greatly affect their function.

Key words: adaptive fetal programming, maternal inflammation

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