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Title

Infertility and Leydig Cell Adenomas Subsequent to Laparoscopic Fowler-Stephens Procedure in Rats: Morphological, Ultrasonographical and Endocrinological Long Term Observations

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Fowler-Stephens procedure (FSP) represents a surgical intervention for cryptorchidism in patients with an impalpable testis. The first step includes ligation of the testicular vessels and during the second step an orchidopexy is performed. The aim of this study was to evaluate the grade of testicular atrophy, possibly resulting in infertility and to estimate the risk of long term testicular tumor formation in rats after FSP. Our results reveal that FSP induced testicular atrophy in 85% with different severity due to inadequate tissue perfusion. In mild to severe testicular atrophy, the seminiferous tubules exhibited apoptosis of germ cells, spermatocytes and spermatids. In addition, enlargement of the interstitial space was present, resulting in the phenotype of Sertoli cell-only syndrome. However, the testicular volume was only slightly reduced compared to the controles. In complete atrophy (47%) a striking volume decrease was accompanied by necrosis of the seminiferous epithelium and marked tubular microlithiasis in the central portion of the residual testis. Most interestingly, in the contralateral testis mild or severe atrophy could be demonstrated very early (45 days) after FSP.. In mild atrophic testis intact spermatogenesis and formation of spermatozoa was preserved, whereas in severe or complete atrophy loss of germ cells resulted in infertility. Leydig cell hyperplasia could be found either in mild or severe atrophic testis in the form of distinct single or multiple Leydig cell nodules which were randomly distributed and finally reached a typical of adenoma size with focal or multiple central necrotic areas. 12 months after FSP adenomas were also seen in the contralateral testis (30 %). In complete atrophy Leydig cell hyperplasia could be demonstrated 3 months after FSP . Leydig cell proliferation, mast-cell invasion and angiogenesis was restricted to the peripheral zone of the testis supplied by collateral perfusion. In order to evaluate the risk and progress of tumor formation, in a second series of experiments FSP combined with removal of contralateral testis was analysed. Our data showed that complete testicular atrophy always paralleled early Leydig cell hyperplasia at 45 days after FSP and 12 months later adenoma marked the peripheral testicular zone. The sonographic examination proved to be of great diagnostic value, since complete atrophic stages could be clearly distinguished and tumor formation at late stages identified. The determination of the serum level of inhibin B confirmed the sonographic and morphological data and offered a very sensitive marker to evaluate the impairment of spermatogenesis. In conclusion, in rats FSP appears as a highly risky method inducing infertility and testicular tumor formation.