Insulin-like factor 3 emerges from the shadow of testosterone as a Leydig cell biomarker

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Insulin-like factor 3 (INSL3) is a peptide secreted by testicular Leydig cells and to a smaller extent by follicular theca cells. It acts via a G-protein-coupled receptor that is expressed in several organs, including bone, brain, kidney, muscle, epididymis, gubernaculum and germ cells. Its functions are not entirely known, but the gene modifications of mice have shown that it is necessary for testicular descent and it is one of the survival factors for germ cells (1, 2). It can also be used as a marker of Leydig cell function in fetal and perinatal period, which can help to identify whether a developing gonad is a testis when only the Leydig cells can produce it. Later it can be used to analyze testicular activation in early puberty as shown by Albrethsen et al. in this issue of *The Journal of Clinical Endocrinology and Metabolism* (3).

Albrethsen and coworkers have developed a new liquid chromatography-tandem mass spectroscopy-based method for measurement of INSL3 (4) that was shown to work as a good biomarker of Leydig cell function (5). Luteinizing hormone (LH) stimulates differentiation and hormone production of Leydig cells. In puberty the LH increase is most often the first change observed in reproductive hormone levels, followed by INSL3 and testosterone (3). The serum levels of INSL3 show less diurnal variation than those of testosterone, and INSL3 concentrations do not depend on obesity like those of testosterone (5). These features make the interpretation of INSL3 results easier than those of testosterone. Boys with constitutional delay of growth and puberty can be treated with small doses of testosterone to induce the secondary signs of puberty. INSL3 can serve as a useful biomarker of Leydig function in these boys, because the testosterone measurements are not informative in this situation.

INSL3 assays are not yet in wide clinical use, although this adds to our repertoire to analyze the function of the testis and particularly of Leydig cells. The emerging role of INSL3 in bone and muscle metabolism may also add to the need for INSL3 measurements (6). More research is needed in this area. INSL3 concentrations decline by aging (5), which may contribute to development of osteoporosis and sarcopenia (6). Since INSL3 is produced by theca cells, it can be used to monitor

the number of growing follicles and prediction of their loss (7). INSL3 receptor is located in the oocyte and functions against apoptosis (2). Reliable and robust hormone assays are essential to gain more information about the significance of INSL3 in human health and disease.

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