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Invited Editorial

Differential diagnosis of elevated human chorionic gonadotropin in women

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Measurement of human chorionic gonadotropin (hCG) in serum and plasma is most commonly used in the early detection and monitoring of pregnancy and, in combination with other parameters, in the evaluation of the risk of trisomy 21 (Down syndrome).

hCG levels may be elevated in a wide range of other situations, including from pituitary production in menopause and conditions such as gestational trophoblastic disease and neoplasia, ovarian and extra-ovarian germ cell tumours. Many other non-germ cell neoplasms may also secrete hCG, occasionally leading to diagnostic difficulty. In the context of investigating suspected neoplasia, hCG measurement is not used for screening but is of value in diagnosis, prognosis, monitoring treatment and detecting recurrence.

hCG is a glycoprotein hormone which comprises two noncovalently bonded subunits. The alpha subunit is common to the glycoprotein hormones thyroid-stimulating hormone (TSH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH). The beta subunit confers functional specificity. Multiple forms may be found in the serum and urine, including the intact hormone, each of the free subunits, iso-hormones and, following degradation in the kidney, a core fragment which is measured in urine hCG tests. There are a large number of commercial serum immunometric assays, using a fixed antibody to bind hCG and a second labelled antibody to confirm its presence. Methods that detect hCG and hCG beta together are mainly used for measurement of hCG-like immunoreactivity in serum and plasma and this of importance when considering the potential causes of elevated hCG values beyond pregnancy since moderately elevated levels can be identified only with a specific and sensitive beta-hCG assay.

In gestational trophoblastic disease, hCG values may be mildly raised in partial hydatidform molar pregnancies, markedly raised in complete hydatidiform molar pregnancies and persistently elevated following primary evacuation in invasive and metastatic hydatidiform moles. Amongst gestational trophoblastic neoplasms, mildly to moderately raised values are seen in up to 80% of epithelioid trophoblastic tumours and placental site trophoblastic tumours [1]. Gestational choriocarcinoma is associated with a highly elevated serum hCG level appearing weeks to years following pregnancy, usually 1–3 months after term delivery [2]. Mixed trophoblastic tumour, which is characterised by the presence of a mixture of two or three histological types of gestational trophoblastic neoplasia, may show slightly or moderately elevated values depending on the components present. High levels are mostly observed in women with lung metastasis.

hCG values may be elevated in a range of ovarian and extra-ovarian germ cell tumours, including non-gestational choriocarcinoma, dysgerminoma (particularly when the tumour contains syncytiotrophoblastic giant cells), embryonal carcinoma and mixed ovarian germ cell tumour with a choriocarcinoma or dysgerminoma component. Exceptionally, raised values have also been described in association with mature teratoma. Consequently, it is important that the examining pathologist has knowledge of the results of tumour marker investigations at the time of reporting to ensure that sampling is sufficiently directed to identify the range of tumour components present.

Many non-trophoblastic and non-germ cell neoplasms also produce hCG, which may have a functional paracrine effect, for example inhibiting apoptosis, promoting angiogenesis and suppressing macrophage activity. In this circumstance, the coordinated secretion of alpha and beta subunits may be disturbed, resulting in a disproportionate production of either free alpha or free beta subunits. Imbalanced or selective production of hCG alpha subunits has been reported in a range of neuroendocrine tumours. Production of hCG beta subunits is a more common phenomenon that has been the subject of many single case reports and fewer larger case series, where many authors suggest it represents an adverse prognostic factor. Raised hCG beta is associated with a wide variety of tumours, including carcinoma of cervical, endometrial, ovarian, breast, lung, thyroid, pancreatic, bladder, kidney, biliary, liver and gastrointestinal origin, a wide variety of sarcomas, and myeloma [3].

hCG beta production by such tumours is associated with a variety of phenotypic features. Carcinomas with otherwise typical morphologic features may express and secrete hCG either from the whole tumour or from a subclone of undifferentiated cells. The presence of hCG within the tumour tissue may be confirmed with immunochemistry in diagnostic surgical pathology practice (and indeed may also occasionally be detected in occasional cells within an otherwise typical tumour). Alternatively, a somatic tumour may develop a choriocarcinomatous

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component which produces hCG. These rare and aggressive tumours are thought to arise as a result of de-differentiation or transdifferentiation of a primary adenocarcinoma. This has most often been described within the stomach but may arise elsewhere in the digestive tract (gastrointestinal carcinoma with choriocarcinomatous component, GACC) [4]. Conversely, the possibility of a somatic malignancy arising in a mixed germ cell tumour, perhaps affected by sampling limitation, must also be considered in the differential diagnosis.

A variety of other uncommon situations may give a positive test result, including the presence of heterophile antibodies (both autoantibodies and those produced following exposure to animal products) which may interfere with the assay and in some assays rheumatoid factor or IgA deficiency [5].

Elevated hCG values are seen in multiple conditions, with a positive result raising a broad range of differential diagnoses. Where investigation requires tissue sampling, results of all investigations are valuable in formulating a final diagnosis.

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