Invited critical review

Using an algorithmic approach to secondary amenorrhea: Avoiding diagnostic error

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ABSTRACT

Secondary amenorrhea in women of reproductive age may be an indication of an undiagnosed, chronic condition and appropriate treatment is dependent upon accurate diagnosis of the underlying etiology. A thorough clinical assessment and a few common laboratory tests can easily identify the most frequent causes of secondary amenorrhea. However, once these have been ruled out, the more uncommon pathophysiologies can be difficult to diagnose due to similarities in presentation and appropriate laboratory testing and inter-pretation become critical. In these cases, misdiagnosis is unfortunately common and often the result of poor laboratory utilization in the form of a failure to employ indicated tests, the use of obsolete tests, or erroneous interpretation in the face of interfering factors or co-morbidities. Consequently, the algorithmic approach to laboratory evaluation in the context of secondary amenorrhea described in this review can minimize the risk of diagnostic error as well was decrease test volume, cost, and time to diagnosis.

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1. Introduction

Approximately 5% of women of reproductive age will experience secondary amenorrhea [1]. In women who had previously experienced regular menstrual cycles, secondary amenorrhea is the absence of menstruation for three months [1]. In women who had previously experienced irregular menstrual cycles, secondary amenorrhea is the absence of menstruation for a year (12 months) [1]. While short-term absence of menses is rarely a cause for concern, amenorrhea of longer duration may indicate the presence of disease or a chronic condition that, left undiagnosed, could cause obesity, sexual dysfunction, infertility, osteoporosis, endometrial hyperplasia, or endometrial cancer. Secondary amenorrhea is a symptom that can be caused by many pathological states and some patients will not demonstrate an obvious etiology, therefore, correct diagnosis requires a systematic evaluation.

Evaluating a patient for secondary amenorrhea and its underlying cause begins with a careful history and physical examination. Family

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history of genetic anomalies, diabetes, thyroid disease, etc. can be especially helpful in reaching a correct diagnosis and often will greatly narrow the differential in these patients. Physical examination is primarily performed to rule out any sort of anatomical cause, but can be critical in identifying other causes as well. For example, overall physical condition and body mass index (BMI) can be helpful in identifying functional hypothalamic amenorrhea, also known as "the female athlete triad". Furthermore, signs of hirsutism or virilization can be indicative of polycystic ovary syndrome (PCOS). Nonetheless, laboratory testing is necessary to definitively diagnose the underlying cause of secondary amenorrhea.

2. Laboratory investigation

The most common causes of secondary amenorrhea can be easily identified and/or ruled out with laboratory testing of human chorionic gonadotropin (hCG), thyroid stimulating hormone (TSH), luteinizing hormone (LH), follicle stimulating hormone (FSH), and prolactin levels as discussed below (Fig. 1). Once these causes have been ruled out, more complex laboratory investigation becomes necessary. Approximately 44% of diagnostic errors are made at the level of laboratory testing [2]. In some cases, the required follow-up testing is not ordered at all or, when it is, tests that are obsolete or even inappropriate may be included [3,4]. With the number of orderable laboratory tests increasing at an alarming rate, it can be a challenge for front-line clinicians to maintain familiarity with tests that are not utilized frequently. Unfortunately, in the context of secondary amenorrhea misdiagnosis of the underlying pathology is not infrequent [5–9]. An algorithmic approach to the laboratory evaluation of secondary amenorrhea, in which negative results for first-line tests will reflex to more complex testing, would simplify ordering for the physician and would be more convenient for the patient [10,11]. This approach would also decrease costs as only one office visit would be required even if more complex testing was needed. Furthermore, the length of time to results and diagnosis
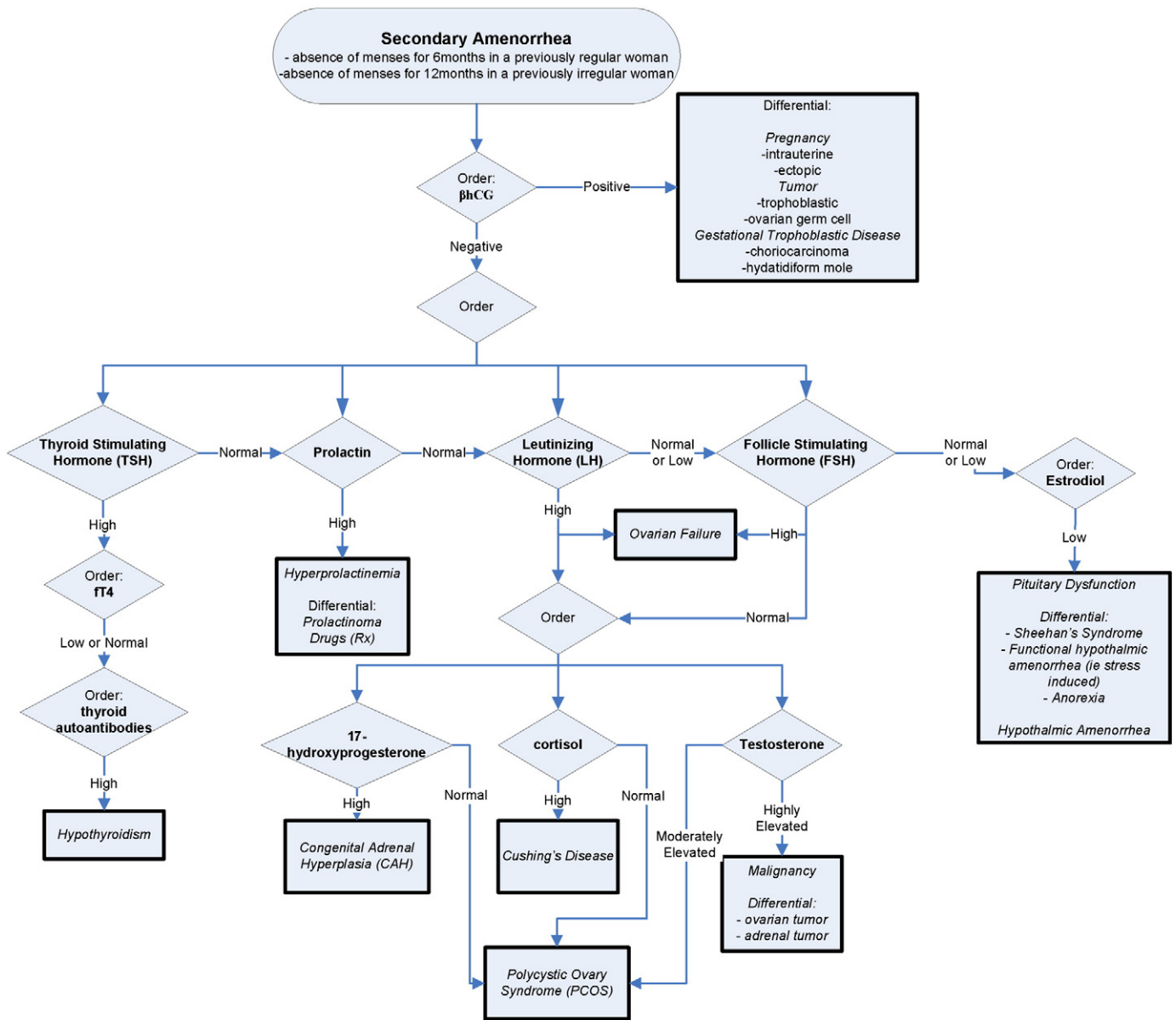
Fig. 1. Algorithm for laboratory evaluation of secondary amenorrhea. Laboratory investigation of secondary amenorrhea should be done in a step-wise fashion. The suggested order of evaluation is shown here and it is recommended that a panel of basic tests be performed at the initial visit to allow more specific testing, or perhaps a diagnosis, upon the following visit in the secondary care setting. This figure represents a simplified schematic of recommended laboratory investigations and clinical correlation is necessary for accurate diagnosis.