Review Article

Emergency diagnostic testing in pregnancy

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Abstract: Emergency diagnostic testing is challenging in pregnancy, whereby some parameters may be modified by the pregnancy and, on the other hand, other laboratory tests are essential for monitoring pregnancy and for diagnosing its potential complications. Owing to a number of physiological adaptations which develop throughout physiological pregnancy, clinically significant changes may develop in the reference ranges of some laboratory tests such blood cell count, urea, creatinine, thyroid hormones, screening hemostasis tests and D-dimer. Reliable evidence is then accumulating that some specific tests may be very useful for diagnosing or ruling out pregnancy-related disorders, especially preeclampsia and even pregnancy-induced hypertension. Therefore, this article aims to provide a concise overview on the significance of emergency diagnostic testing in pregnancy.

Keywords: Emergency medicine; laboratory medicine; diagnostic testing; pregnancy; abdominal pain

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Introduction

Owing to a number of physiological adaptations developing throughout normal pregnancy, several changes in reference ranges of laboratory tests tend to occur, as recently emphasized in some seminal articles (1,2). This evidence assumes pivotal significance for clinicians, especially for those who are not expert or specialized in pregnancy-related problems, but may be still challenged by their management. Among many of these healthcare professionals, emergency physicians (EPs) are particularly vulnerable to misinterpreting the results of laboratory testing in pregnant women presenting to the emergency department (ED) for a variety of symptoms, which can be either related or non-related to pregnancy itself. The most frequently used urgent laboratory tests, whose values are often modified during pregnancy, are summarized in *Table 1* (1,2).

Notably, cardiac biomarkers are also frequently used in the ED, but no important variations in their reference values have been described so far to the best of our knowledge. Cardiac troponins (cTns) are not essentially affected by pregnancy when measured with the former "contemporary-sensitive" immunoassays (8). An interesting study has recently been published using the novel high-sensitivity (hs) immunoassays. Briefly, Ravichandran *et al.* recruited a total number of 880 women, 14%, 24%, 47% and 10% of whom were in the first, second, third trimester and postnatal period, respectively (3). Overall, hs-cTnI concentration was measurable in the vast majority of these women, values exceeding the conventional 99th percentile of that specific immunoassay in only 2% of cases. Interestingly, patients who developed preeclampsia and even pregnancy-induced hypertension were found to have increased hs-cTnI values, thus confirming that cTns may be a valuable marker for predicting these pregnancy-related complications. This conclusion is supported by data obtained in another small-series case study involving 60 pregnant women published in form of an abstract by Ayachi *et al.*, who also showed that the values of hs-cTnI were higher in women with preeclampsia than in those without (9).

Table 1 Variation of some laboratory parameters throughout pregnancy (1-7)

	Non pregnant women	Pregnant women		
		1st trimester	2nd trimester	3rd trimester
Arterial pH	7.38–7.42	–	–	7.39–7.45
Arterial pO_2 (mmHg)	83–108	105–106	105–106	101–106
Arterial pCO_2 (mmHg)	38–42	28–29	26–30	25–33
Arterial HCO_3 (mmol/L)	22–26	16–22	16–22	16–22
Sodium (mmol/L)	136–146	133–148	129–148	130–148
Potassium (mmol/L)	3.5–5	3.6–5	3.3–5	3.3–5.1
Calcium (mmol/L)	2.2–2.6	2.2–2.6	2–2.25	2–2.4
Albumin (g/L)	35–55	32–43	27–37	23–34
Alkaline phosphatase (U/L)	20–140	60–140	65–192	88–380
Alanine aminotransferase (U/L)	15–30	12–27	11–27	10–25
Aspartate aminotransferase (U/L)	13–29	12–27	11–27	10–24
Lactate dehydrogenase (U/L)	100–190	140–250	140–300	140–300
Total bilirubin (μmol/L)	7–19	7–17	6–16	6–16
Creatinine (μmol/L)	50–90	40–70	40–80	30–90
Urea (mmol/L)	2.5–7.1	2.5–4.3	1.1–4.6	1.1–3.9
Hemoglobin (g/L)	120–140	100–120	100–120	100–120
Leukocytes ($\times 10^9$/L)	3.5–9.1	5.7–13.6	5.6–14.8	5.9–16.9
D-dimer (μg/L)	220–740	50–950	320–1,290	130–1,700

Unlike cTns, the values of b-type natriuretic peptide (BNP) remain basically unchanged during non-complicated pregnancy (namely, non-hypertensive pregnancy), but transiently increase between 2- to 3-fold in the 2 following days after delivery, a variation that has been attributed to the physiological changing in mother circulation (10).

Although the assessment of arterial blood gases (ABGs) is an essential practice in emergency medicine, this test is one of those mostly affected during pregnancy and thus requires especial thoughtfulness and skill in terms of results interpretation (1,2,11). For example, due to reduced reserve in bicarbonates and consequent lower buffer capacity, both diabetic and starvation ketoacidosis may develop in patients with decreased blood glucose levels and after relatively brief periods of fasting (even less than 16 h), particularly in the second and third trimesters (4,12).

Slight decreases in sodium and potassium levels are usually meaningless in normal pregnancy, while severe hyponatremia can occur in pre-eclampsia, and severe hypokalemia can occur in hyperemesis gravidarum (13,14). Hypernatremia and hyperkalemia are both very rare in physiological pregnancy (1,2). A substantial increase of renal plasma flow and glomerular filtration rate also occurs (i.e., approximately 60% compared to pre-pregnancy values), starting early in first trimester and being accompanied by a concomitant fall of approximately 30% of both serum creatinine and urea (15). Importantly, it shall hence be always considered that apparently "normal" values of these tests may mask the presence of renal dysfunction when their pregnancy-related variation is not known or appreciated. Albumin and total bilirubin values may also be decreased for almost the same reason throughout pregnancy, whilst the activity of most enzymes remains unvaried or tends to gradually increase by the end of the pregnancy, especially that of alkaline phosphatase (ALP) (*Table 1*) (5,16).

Due to structural similarity between human chorionic

gonadotropin (hCG) and thyroid stimulating hormone (TSH), the former molecule can bind to—and thereby stimulate—the TSH receptor, thus causing a modest increase of free thyroxine (fT4) levels and a consensual decrease of TSH (17). This important pathway shall also be clearly acknowledged when evaluating suspected hyperthyroidism in pregnancy.

A slight decrease in hemoglobin level, starting early during the first trimester, does not usually needs clinical attention (i.e., the lower limit of the hemoglobin reference range is typically 120 g/L in women, but can be as low as 100 g/L during pregnancy), whilst a significant increase in the white blood cells (WBC) count, approximating 16×10^9/L in the third trimester, can be a confounding factor when investigating patients with coexisting pathological conditions, such as in those with non-specific acute abdominal pain (18). Notably, the platelet count also tends to gradually decrease in pregnancy, even if the number typically remains within acceptable limits (i.e., in only 5–10% of pregnant women it may fall below 100×10^9/L) (6).

Both the activated partial thromboplastin time (APTT) and prothrombin time (PT) have been reported to be slightly reduced (i.e., between 10–20%) during pregnancy, but even this variation lacks clinical significance (7). Unlike these hemostasis tests, a continuous increase of D-dimer levels is always seen throughout pregnancy, with values exceeding the conventional upper reference limit (URL) in 96–100% of pregnant women during the third trimester (19,20). This event is cause of an ongoing debate as to whether D-dimer shall be used for diagnosing and, especially, for ruling out episodes of venous thromboembolism (VTE) in pregnancy. Given the huge heterogeneity of D-dimer variation in pregnant women, no reliable pregnancy-related cut-offs have been identified so far, neither within specific trimesters (21). The use of this test may hence lead to misdiagnosing thrombosis in pregnancy, and we reasonably argue against its use in this specific clinical setting due to its low reliability and high risk of false positive results.

The measurement of human chorionic gonadotropin β (β-hCG) remains the milestone for diagnosing pregnancy, but this test may also be clinically useful in a variety of different pathologic conditions (namely pregnancy-related disorders), as well as for prenatal screening and in the diagnostic approach of patients with gynecological cancers, as extensively described elsewhere (22,23). Nevertheless, potential false positive and false negative results may occur, due to both laboratory and clinical issues (22). Several cases of positive β-hCG test in patients with renal impairment (especially those with end-stage renal disease) have been described (24,25). Some different mechanisms have been proposed for explaining this finding, including decreased metabolism and impaired renal clearance, enhanced production of gonadotropins and uremia-dependent variations (26,27).

Pregnancy management in the ED

The two major issues faced when dealing with pregnant women in general EDs are: (I) the kaleidoscope of causes of acute abdominal pain which lead women to the ED; (II) the high percentage of worldwide unplanned or unexpected pregnancies, including in developed Western countries.

Acute abdominal pain is one of the most common complaints leading the general population to the ED, accounting for up to 10% of all ED visits (28). Despite the high frequency and prevalence of non-urgently manageable cases, abdominal pain may be the main symptom of a large number of underlying pathologies, so that challenges in differential diagnosis may be causes of forensic litigations and adverse outcomes (29). In young women, gynecologic disorders (e.g., ectopic pregnancy, endometriosis, and pelvic inflammatory disease) are other diseases that shall be considered in the differential diagnosis (30). Since the investigation of the underlying cause of acute abdominal pain may span across many different medical disciplines such as gynecology, urology, surgery and internal medicine, expert assessment is an essential preamble in the care of these patients.

The ED utilization in pregnancy varies widely, typically between 21–49%, and is also characterized by higher rate of return ED visits compared to non-pregnant patients (31). Notably, the reason why ED care is very frequent in pregnant women is that direct contact with obstetrical care providers may have not been established at the early stage of pregnancy (32). A recent German observational study showed that the most frequent reason for ED use among pregnant women was "pain" (i.e., 28.3% of all cases), followed by cervical insufficiency (19.7%). Overall, 36.3% of all patients were then hospitalized for ensuing clinical management, whilst 58.6% could be discharged. It was hence concluded that the high volume of patients making non-urgent use of ED services indicates a potential uncertainty in symptoms interpretation (33).

Despite many advances have been recorded in reproductive health, nearly half of all pregnancies is still

unplanned, or at least unexpected, in Western countries (34), so that many of these patients are firstly evaluated in an ED because complaining for apparently different urgent issues, especially abdominal pain or vomit (35). Other patients, admitted to the ED for different types of trauma, are occasionally found pregnant after undergoing testing for radioprotection policy (i.e., pregnancy testing before X-rays exposure) (35).

The diagnosis of pregnancy is hence based on a multifaceted approach, encompassing essentially clinical history, physical examination, laboratory investigation(s) and, occasionally, diagnostic imaging (i.e., ultrasonography). Unplanned pregnancy has then been associated with a variety of factors, basically including a significant delay in recognizing pregnancy, low maternal socioeconomic status, partner violence, low maternal compliance with nutrition and lifestyle recommendations for pregnancy (e.g., folic acid supplementation for preventing neural tube defects), insufficient breastfeeding, as well as postpartum depression (36). Some Authors have hence identified some critical issues to drive emergency medicine-based adolescent sexual and reproductive health research, addressed for improving health outcomes of unintended pregnancy, as well as for reducing the risk of HIV and other sexually transmitted infections (37). EPs play a pivotal role in diagnosing these conditions, as well as in attempting to prevent their complications.

Due to increasing availability of bedside ultrasound in EDs, this diagnostic technique is now frequently used for evaluation of female patients presenting with acute abdominal pain. Therefore, many algorithms guiding the evaluation of this condition, along with vaginal bleeding, in early pregnancy conventionally include the results of quantitative total β-hCG serum measurement and pelvic ultrasonography. Notably, when facing acute abdominal pain the EPs still need to go through a complete differential diagnosis workup. Despite remarkable improvements in the diagnostics approach of this condition, taking profit from the use of ultrasonography and CT, non-specific abdominal pain (NSAP) remains the leading diagnosis, representing approximately one fourth to one third of all cases depending on selection criteria used in the individual studies and local organization (29).

The widespread use of sophisticated imaging techniques brought only marginal improvements in diagnostic specificity during the last decades, especially for surgery-needing conditions (38). Moreover, this practice has not generated a substantial reduction of admission rate (28). Despite reliable evidence of scarce diagnostic performance, plain abdomen X-ray is still widely prescribed in as many as 35–45% of all cases of acute abdominal pain (39), thus contributing to diagnostic waste and confusion, as well as to potentially dangerous irradiation of embryos and/or fetuses. Fortunately, at least in suspected pregnancy as a cause of ED visit, β-hCG gives a substantial diagnostic support, displaying a value that is similar to that of cTns in evaluating chest pain patients (40).

Conclusions

Emergency diagnostic testing in pregnancy shall still be considered a challenging issue whereby some laboratory parameters may be modified by the pregnancy and, on the other hand, some laboratory tests are essential for pregnancy monitoring and for diagnosing its potential complications. These facts even strengthens the need of an unavoidable close partnership that is now required between EPs and the clinical laboratory (41), especially for troubleshooting those cases—such as abdominal pain in women—for which laboratory resources must be very accurately selected (42).

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