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ORIGINAL ARTICLE

Evaluation of point-of-care maternal venous lactate testing in normal pregnancy

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Abstract

Objective: There is little information about whether the established non-pregnant adult venous lactate reference range is appropriate for pregnancy. This prospective observational study examined whether the non-pregnant adult reference range is appropriate during pregnancy.
Methods: Women attending for routine prenatal appointments or elective cesarean delivery in a tertiary hospital were recruited. Clinical details were recorded and venous lactate concentration was measured using a point-of-care (POC) device.
Results: Of the 246 women, 199 were 6–18 weeks' gestation and 47 were 36–42 weeks' gestation. Mean lactate concentration was within the non-pregnant reference range in early and late pregnancy (0.86 SD ± 0.46 mmol/L and 1.15 SD ± 0.40 mmol/L, respectively). The mean time between phlebotomy and result was 6.1 SD ± 1.7 min. There was no correlation between lactate levels and either maternal age or time interval from tourniquet placement to lactate measurement. In women of 6–18 weeks' gestation positive bivariate relationships were found between lactate and BMI ($p = 0.03$, $r = 0.158$), earlier gestational age ($p = 0.04$, $r = -0.145$), and smoking ($p = 0.01$, $r = 0.183$), but these were not found in late pregnancy.
Conclusions: The venous lactate reference range for the non-pregnant adult may be applied in pregnancy. Further studies should examine lactate dynamics in labor and postpartum.

Keywords

Critical illness, maternal medicine, obstetric physiology

History

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Introduction

Serum lactate has emerged as an important biomarker in the management of adults with critical illness. Studies conducted in the setting of critical care medicine and emergency medicine have shown the utility of both arterial and venous lactate measurements as an aid to triage, as a predictor of mortality and as an indicator of response to treatment [1–3]. The *Surviving Sepsis Campaign* recommendations for the management of sepsis advise the use of lactate measurements to help identify severe sepsis and septic shock, and as a guide to subsequent therapy [4]. Lactate-guided therapy has been shown to decrease mortality in a broad range of medical conditions among critically ill Intensive Care Unit (ICU) patients [3,5]. Lactate measurement is also useful in the differentiation of major from minor trauma cases in the emergency department (ED) triage setting [6].

The normal plasma lactate concentration for the non-pregnant adult is 0.3–1.3 mmol/L, with concentration representing the balance between production and clearance of the metabolite [7]. Liver metabolism accounts for 70% of lactate clearance with the remainder converted to pyruvate in skeletal and cardiac myocytes and 5% undergoing renal excretion [7]. The *Surviving Sepsis Campaign* guidelines for sepsis in non-pregnant adults cite lactate >1.0 mmol/L as abnormal [4]. The Royal College of Obstetricians and Gynaecologists' guideline on bacterial sepsis in pregnancy includes lactate ≥4.0 mmol/L as one of its diagnostic criteria for severe maternal sepsis [8].

The physiological changes of pregnancy include elevation in the leucocyte count and hemodynamic adaptations of vasodilatation, increased cardiac output and increased glomerular filtration rate [9]. If serum lactate measurement is to be used in the diagnosis and management of critical illness during pregnancy, and considering the divergence in definitions of normal cited above, it is important to ascertain the normal range for pregnancy. However, there is a dearth of evidence regarding normal maternal lactate concentration in pregnancy.

The purpose of this prospective observational study was to examine whether the established non-pregnant adult venous lactate reference range may be applied in normal pregnancy so that the clinical management of the critically ill pregnant woman is based on the appropriate interpretation of venous lactate results.

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Table 1. Characteristics of the study population ($n = 246$).

Characteristic	Early pregnancy* (n=199)	Late pregnancy† (n=47)	p
Mean lactate, mmol/L (range)	0.86 ± 0.46 (0.30–3.47)	1.15 ± 0.40 (0.51–2.50)	<0.001
Mean age, years (range)	30.4 ± 5.6 (18–42)	34.3 ± 4.3 (25–45)	<0.001
Mean gestation, weeks (range)	12.1 ± 1.4 (6.4–17.4)	39.0 ± 0.9 (36.7–41.1)	<0.001
Mean BMI‡, kg/m^2 (range)	26.7 ± 6.3 (18.1–60.3)	25.4 ± 4.0 (18.0–34.7)	0.17
BMI >29.9 kg/m^2, % (n)	21.6 (43)	12.8 (6)	0.22
Current smoker, % (n)	13.6 (27)	0.0 (0)	0.01
Fasting time, hours (range)	Not available	13.7 ± 3.7 (6.0–20.0)	–

*Gestational age 6–18 weeks.

†Gestational age 36–42 weeks.

‡Body Mass Index.

Methods

The Coombe Women and Infants University Hospital is a tertiary university teaching hospital. It accepts women from all socio-economic groups and from both urban and rural regions. It is one of the largest maternity hospitals in Europe, delivering over 8000 infants weighing ≥500 g per annum [10].

The study was conducted between May 2014 and January 2015. Women were recruited while attending the hospital for routine prenatal appointments in the first and second trimesters or for elective cesarean delivery in the third trimester. Written informed consent was obtained and socio-demographic and clinical details were recorded. Body Mass Index (BMI) was calculated following height and weight measurement in a standardized way by a trained midwife. Obesity was defined as BMI >29.9 kg/m^2. An uncomplicated ongoing pregnancy, the absence of either a confirmed diagnosis or symptoms of infection, the absence of preexisting metabolic disease or other medical conditions and, in late pregnancy, the absence of signs or symptoms of labor, were confirmed before women were included in the study. Women with a diagnosis of gestational diabetes mellitus were excluded. Sonographically confirmed gestational age (weeks and days) was noted and decimalized for the purposes of statistical analysis. Preoperative fasting time was recorded for the women attending for cesarean delivery.

Women unable to provide written informed consent and those with medical conditions or complications of pregnancy, and women taking medication, were excluded from the study. All investigators were trained in use of a point-of-care (POC) device and were fully competent in phlebotomy before commencement of the study. A research midwife (R.H., M.N.) or a resident grade anesthesiologist (J. F.) obtained a venous lactate sample by venepuncture. This was at the same time as routine prenatal blood testing for the women recruited during their prenatal appointments. For the women recruited when attending for elective cesarean delivery the venous sample was obtained during placement of an intravenous catheter by the anesthesiologist on arrival in the operating theater. The sample was analyzed using a POC testing device (*i-STAT 1 Wireless analyzer [300 series]* and *CG4+* test cartridges, Abbott Point of Care Inc., Princeton, NJ). The time intervals from tourniquet placement to filling of specimen bottle, insertion of the testing cartridge into the testing device and test result were measured using an electronic stopwatch. The operating procedure recommended by the manufacturer was followed by all three investigators involved in sample testing. Hemoglobin and hematocrit concentrations in samples obtained during the same phlebotomy episode were retrieved from the hospital's central laboratory database.

Written informed consent was obtained from all study participants and approval was granted by the Hospital Research Ethics Committee (Research Ethics Committee reference numbers 27–2013 and 19–2014). Statistical analysis was performed using a statistical analysis program (*SPSS Statistics for Windows Version 20.0*, IBM, Armonk, NY). Bivariate analysis was conducted using two-tailed Pearson's correlation coefficient where $p < 0.05$ was deemed significant. Linear regression was performed for multivariate analysis.

Results

A total of 246 women were recruited. The characteristics of the study population are shown in Table 1. Of the 246, there were 199 women in early pregnancy (6–18 weeks' gestation) and 47 women in late pregnancy (36–42 weeks' gestation). The mean gestation for women in early pregnancy and late pregnancy was 12.2 weeks and 39.0 weeks, respectively. The mean time between beginning phlebotomy and reading the result was 6.1 SD ± 1.7 min. The mean lactate concentration was 0.86 SD ± 0.46 mmol/L in early pregnancy and 1.15 SD ± 0.40 mmol/L in late pregnancy.

There was no correlation between lactate levels and maternal age, parity or time from placing the tourniquet to lactate measurement. There was no relationship between fasting time and lactate concentration among the women attending for elective cesarean delivery. In women of 6–18 weeks', gestation positive bivariate relationships were found between lactate and BMI ($p = 0.03$, $r = 0.158$), earlier gestational age at measurement ($p = 0.04$, $r = -0.145$), and smoking ($p = 0.01$, $r = 0.183$), but these relationships were not found among the women in late pregnancy.

There were 10 (4.1%) women with a lactate value of >2.0 mmol/L. Of the 10 women with a lactate value >2.0 mmol/L, the mean hemoglobin was 124 g/L (range 113–140 g/L) and the mean hematocrit was 0.361 L/L (range 0.338–0.388 L/L). Of the seven women in early pregnancy with a lactate of >2.0 mmol/L, three were smokers, one was a former smoker and three women were obese (32.5, 33.8 and 38.2 kg/m^2 respectively). The three women in late pregnancy with a lactate value >2.0 mmol/L were non-smokers and were not obese.

Discussion

Our study found that maternal venous lactate levels in pregnancy were similar to those in the non-pregnant adult. POC testing meant all results were available soon after venepuncture which may potentially improve decision-making. This information is important for the interpretation of venous lactate results in pregnant women with a critical illness.

Strengths of the study include the objective, sonographic confirmation of gestational age, and the availability of accurate BMI calculations. Only the investigators involved in the study undertook sample testing and all used the same technique. Our study reported venous lactate concentrations across the trimesters of pregnancy, although we acknowledge that we did not obtain lactate values for women with a pregnancy between 18 and 36 weeks' gestation.

We did not have laboratory results of renal or liver function tests available for the women in our study. However, since women with medical conditions and complications of pregnancy were excluded, we have no reason to believe that renal or liver function tests would have been abnormal in a healthy cohort of women. Given that there was no correlation between tourniquet time and lactate concentration it is reasonable to believe that any effect of *in vitro* red cell glycolysis was minimal.

A limitation of the study is the difference in the fasting status of the women in early pregnancy compared with those attending for cesarean delivery. However, there was no relationship detected between fasting time and lactate concentration in the women attending for cesarean delivery. The absence of smokers in the late pregnancy group may be due to smoking cessation over the course of pregnancy. As well as the difference in fasting status, we recognize that our early and late pregnancy groups represent different populations since the women in the former group were attending routine prenatal appointments while the women in the latter group were attending for elective cesarean delivery. In light of the differences between the early and late pregnancy groups, we have not sought to analyze relationships between the two groups. The differences between the populations may account for the absence in the late pregnancy group of the correlation between gestational age and lactate concentration seen in early pregnancy.

The nature of our study design, with opportunistic sampling, meant that we did not have samples from women between 18 and 36 weeks' gestation. We believe, however, that our findings from both early and late pregnancy can give clinicians reassurance when interpreting lactate concentrations in non-laboring pregnant women.

A study of 69 women and their infants in Malaysia examined both maternal and fetal lactate concentration during the active second stage of labor with a focus on the causes of increased fetal lactate concentration [11]. It found that both maternal and fetal lactate increase during the active second stage, with concentrations positively correlated with its duration [11]. Anaerobic metabolism was identified as the main driver of the increase in lactate concentration observed [11].

Lactate concentration has previously been shown to be positively correlated with BMI. A Swedish study in a non-pregnant population found that obese subjects had higher lactate concentrations than lean subjects, with lactate release from adipose tissue identified as the mechanism of this difference [12]. A study in Germany found that lactate concentration increased in a pulsatile fashion in response to nutrient intake, with fluctuations closely related to fluctuations in insulin concentration [13].

Paired sample testing for validation and comparison between the POC method and the standard laboratory method for lactate concentration measurement has been conducted previously. A study in the USA assessed the feasibility and the accuracy of POC venous lactate testing in a cohort of 699 patients attending an ED with suspected infection, with paired samples analyzed in a central laboratory [14]. It showed that POC testing was a reliable and feasible way to measure lactate at the bedside. It also showed that lactate levels measured using a POC device correlated closely with those measured in a central laboratory, although POC lactate measurements were, on an average, 0.32 mmol/L lower than laboratory lactate measurements. The authors postulated that differences in assay techniques and the time delay in transport and in processing in the laboratory may have led to falsely elevated central laboratory measurements [14].

Arterial blood has conventionally been considered the standard for lactate concentration measurement. However, considering the invasive nature and relative technical difficulty of arterial blood sampling, recent studies have examined the correlation between venous and arterial lactate concentration in order to explore venous lactate measurement as an alternative to arterial sampling. An Australian study evaluated 167 paired central venous and arterial samples from 110 patients in ICU and found that agreement between them was good [15]. An ED-based prospective study in France recruited 103 patients and found strong correlation between venous POC and arterial central laboratory measurements [16]. Another ED-based prospective study in Japan recruited 72 patients for venous and arterial lactate measurement and found that venous and arterial values were strongly correlated, with an average difference of 0.27 mmol/L [17].

A systematic review of 33 studies supported the utility of both venous and arterial blood lactate monitoring as a valuable predictor of in-hospital mortality in patients admitted acutely in ED, trauma centers and ICU [18]. Both single lactate measurement and serial lactate measurement were found to be useful [18]. Six studies comparing POC testing were included in the review, with high accuracy for results of POC lactate measurement when compared with laboratory testing shown by a number of studies [18]. The authors of the systematic review viewed arterial blood sampling as the 'gold standard' for measurement of lactate levels, but stated that POC testing using capillary or venous blood increases the accessibility of the test, with minimal risk for the patient and minimal training required for healthcare staff to safely obtain an accurate result [18].

Serum lactate has emerged as a key test both for the initial assessment of critically ill patients and the subsequent monitoring of their response to treatment. A study in the setting of the ICU in the Netherlands ($n = 348$) showed that lactate measurement on admission and subsequent treatment aimed at reducing lactate levels resulted in reduced hospital mortality and reduced length of ICU stay when compared

with no lactate monitoring [3]. A study in the setting of the ED in the USA ($n = 830$) showed the ability of venous lactate to predict mortality in patients presenting with severe sepsis, independently of clinically apparent signs of organ dysfunction or hypotension [1]. In light of this, the authors questioned the traditional view of serum lactate solely as an indicator of tissue hypoperfusion and postulated that it may also be a biomarker of inflammation.

Based on the data from our preliminary study in healthy women, the non-pregnant adult venous lactate reference range is appropriate for early and late pregnancy. POC venous lactate testing provides results immediately after phlebotomy. The clinical circumstances in which POC maternal lactate measurement should be used and its value in the setting of critical care require further elucidation. In addition, lactate dynamics in labor and in the postnatal period should be assessed in future studies.

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Declaration of interest

A point of care testing device *(i-STAT 1 Wireless analyzer [300 series]*) was provided on loan from Abbott Point of Care Inc. (Europe) along with lactate testing cassettes, free of charge, for use in the study. The authors report no other declarations of interest.

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