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Biochemical Changes in Pregnancy-What Should A Clinician Know?

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Abstract

Pregnancy is a time of dramatic physiological change. Common biochemical tests measured by clinicians may be changing during this time and understanding these changes is important for correct interpretation. To assist clinicians interpret biochemical tests in pregnancy, laboratories may provide specific pregnancy reference intervals. These can be developed from the literature but confirmation of local reference intervals by laboratories is also important.

Understanding the changes that occur to fluid status, renal function, salt and water handling in pregnancy clarifies why serum sodium, creatinine and osmolality levels change. Serum sodium and osmolality fall in pregnancy and may be below non-pregnant reference intervals and be normal for this physiologic state. Serum creatinine similarly is generally lower in healthy pregnancy than in non-pregnant women. As such creatinine values at the upper end of normal non-pregnant ranges or mildly increased for a non-pregnant woman may represent significant renal dysfunction in pregnancy and should be carefully reviewed. In the same way, an appreciation of the changes in insulin resistance and carbohydrate metabolism will help clinicians understand why blood glucose levels change in normal pregnancy and why glucose tolerance may be altered. Variable glycosuria is common in pregnancy and is a poor indicator of glycaemic status. Fasted blood glucose levels are often lower in healthy pregnancy than the non-pregnant woman whereas post prandial glucose levels rise in pregnancy. This rise in glucose in the non-fasting state is secondary to increased insulin resistance and pregnancy hormones and this trend in excess may manifest in gestational diabetes.

Keywords: Pregnancy; Biochemistry tests; Reference intervals; Serum sodium; Renal function

Introduction

During pregnancy dramatic changes are occurring in the developing fetus and in the pregnant woman [1]. Significant changes to maternal biochemistry are part of that process and reflect the normal physiology of pregnancy. Understanding the underlying causes of these changes and that different reference ranges that may be appropriate in pregnancy is important for clinicians who care for pregnant women. Two of the main areas where physiological changes result in altered biochemistry results in pregnancy will be described in this review. These include firstly changes in sodium, water balance and renal function [2-4] and secondly, alterations in carbohydrate metabolism as evidenced by changes in insulin resistance and glucose levels.

Discussion

Role of pregnancy specific reference intervals

Clinicians should be aware of the role of pregnancy specific reference ranges intervals and how these can assist correct diagnosis and management in pregnancy. Reference intervals provide the range of results found in healthy individuals. As healthy physiology changes in pregnancy, different reference intervals may be needed. Appropriate pregnancy reference intervals help clinicians to avoid interpreting normal results as pathological and help them to identify when results are truly abnormal [5,6]. This approach reduces confusion [7] and may optimise patient care.

For a laboratory to determine if pregnancy reference intervals are required or not for a specific test the magnitude of change occurring to an analyte must be considered. If there is a significant change in results from non-pregnant to pregnant states than this may warrant a different reference interval [8]. Deciding if a change is significant or not is best decided by clinical outcome [9], but this may not always be possible and so clinical opinion or statistical evidence [8] may also be used. There is detailed literature which now describes and quantifies the changes to common tests in pregnancy [5,6,10-

12] and laboratories should utilise this data and study their own populations to confirm suitable reference intervals for their results.

Reduction in serum sodium, reduced osmolality and reduced serum creatinine

One of the earliest changes in pregnancy, which occurs by 6 weeks, is a change in systemic and renal vascular tone with vasodilation of peripheral and renal vasculature [2-4,13]. This initial vasodilation explains why many subsequent changes of pregnancy including volume expansion, lower serum sodium, reduced haematocrit and reduced serum albumin occur [3]. Because of vasodilation, blood pressure also decreases, cardiac output increases to compensate and there is increased renal blood flow and increased glomerular filtration rate. These changes all result in a reduction in serum creatinine.

Reduction in serum sodium

The changes that occur to serum sodium are as a result of the vasodilation and secondary increase in water and sodium retention and increased plasma volume. Although there is an overall increase in total body sodium during pregnancy, the increased plasma volume and water retention actually result in a reduction in measured serum sodium of between 3-5mmol/L [11]. It is important that clinicians caring for pregnant women are aware that serum sodium slightly below the non-pregnant female reference interval may be quite appropriate and healthy in pregnant women and does not necessarily need to be actively managed. As such, a reference interval that accommodates this change and incorporates the normal lower serum sodium in pregnancy is important. In contrast to the range of 135-145mmol/L which has been proposed as a harmonised reference interval for non-pregnant women and adult men in Australia [14], a lower range of serum sodium 132-142mmol/L may be more appropriate for pregnant women [15].

Reduction in serum creatinine and urea

The vasodilation of the renal blood vasculature is also increases blood flow through the kidneys [13] and results in up to 50% increase in glomerular filtration rate (GFR) [2,3,13,16]. In normal pregnancy serum creatinine levels can be significantly lower (70% of normal) and less than age matched non-pregnant women's levels [13]. Urea levels are also lower in pregnant women and may be 65-70% of usual levels [11]. Once again, it is very important that the laboratory supports the clinician with appropriate reference ranges, which highlight this lower healthy range. For example if the reference interval in non-pregnant women was 45-90umol/L [14], it has been suggested that the reference interval for pregnant women may be in the range of 30-80umol/L [17]. An appropriate lower reference interval in pregnancy would highlight for example, that a creatinine of 90umol/L would in fact be elevated in the context of pregnancy. Given the importance of detecting deteriorating renal function in conditions such as pre-eclampsia, a specific pregnancy reference interval for creatinine would alert clinicians to mild increases in creatinine and impairment in renal function more readily.

Reduced serum osmolality

Another important change to salt and water handling in pregnancy is the re-setting of the osmostat. Osmolality can decrease early in pregnancy, (as early as 5 weeks) and can reach its lowest point at 10 weeks gestation [3,13]. The decrease in osmolality can be up to10mmol/kg and is because vasopressin is secreted at lower osmolality than in non-pregnant women [11,18-20].

Urine and serum glucose, insulin secretion and insulin resistance during pregnancy

Urine glucose a poor marker

The normal renal glucose threshold is variable but is approximately 10mmol/L [21]. In pregnancy, there is not only an increased filtered load of glucose at the kidney but also reduced glucose reabsorption (reduced glucose threshold) in the proximal convoluted tubules resulting in glycosuria [13]. Pregnant women excrete 10 times more glucose in their urine than non-pregnant women and this increased excretion occurs very early in pregnancy and peaks at about 8-11 weeks. The variable glycosuria seen in pregnancy is unrelated to the blood sugar level or gestation but related to reduced reabsorption of glucose, and as such urine glucose is a poor indicator of glycaemic status in pregnancy [22].

Changes in glucose tolerance

Significant changes occur in handling of carbohydrates during pregnancy and these are different in early and later gestation [11]. In early pregnancy, glucose tolerance is normal or slightly improved [23]. Insulin secretion is increased in response to a glucose load with an increase of up to 120% during first trimester of the first phase of insulin response but no change in the second phase insulin response. Sensitivity to insulin is normal or slightly increased. The reason for the increased insulin secretion is unknown but together with increased cortisol, estrogens and progestins results in increase fat synthesis and fat storage [23]. As pregnancy progresses to the 2nd and 3rd trimesters, insulin resistance also occurs. The enhanced secretion of insulin (now both 1st and 2nd phase increases) [24] in response to a glucose load becomes even more prominent with up to 200-250% increase in insulin following a glucose load [25]. However the action of insulin is reduced up to ~50-70% [23-25] and the cause of the insulin resistance is unclear. In most pregnant women the progressive insulin resistance is compensated for by increasing secretion of insulin but where these mechanisms fail to compensate, gestational diabetes ensues [23].

Changes to fasting blood glucose

Most studies report that fasting blood glucose falls by 10-20% in early pregnancy [11]. In the 2nd and 3rd trimesters of

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pregnancy, hepatic glucose production increases and helps meet the needs of the growing fetus. This is because endogenous hepatic glucose production remains sensitive to insulin in contrast to the peripheral insulin resistance. In 3rd trimester the basal glucose remains reduced by ~ 0.5-0.8mmol/L and absolute rates of carbohydrate and glucose utilisation by the mother have increased due to the increasing use of glucose by the fetus. Because of insulin resistance and the rising pregnancy hormones which further exacerbate insulin resistance, there are higher post prandial glucose levels and prolonged glucose peaks following a glucose load [23]. Understanding that insulin resistance is important in 2-3rd trimester explains why laboratory testing for gestational diabetes is performed at around 26-28 weeks generally. Given these significant changes in carbohydrate handling and the importance of detecting gestational diabetes, laboratories should also provide clear guidelines on locally or nationally agreed cut-offs for diagnosis of gestational diabetes.

Conclusion

Significant changes are occurring in pregnant women and these result in lower serum sodium, lower osmolality, reduced serum creatinine and variable changes in urine and serum glucose. Clinicians should be aware that these changes to common laboratory analytes may be normal. If the laboratory provides appropriate reference intervals to highlight these changes these will further assist clinicians in identifying truly abnormal results and provide reassurance when results are "normal" for pregnancy.

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