Biochemical tests in pregnancy

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Summary

Pregnancy is a normal physiological phenomenon with many biochemical changes ranging from alterations in electrolyte concentrations to more complex changes in cortisol and calcium metabolism. The results of biochemical tests during pregnancy may therefore differ from the normal reference ranges so they may be mistakenly interpreted as abnormal. This can lead to unnecessary and potentially dangerous therapeutic actions. If there is doubt about a result, contact the laboratory to ask if the result reflects the physiological changes that occur during pregnancy. Further investigation and treatment can be recommended if appropriate.

Key words: human chorionic gonadotrophin, thyroid disease.

(Aust Prescr 2005;28:98–101)

Introduction

Pregnancy is associated with normal physiological changes that assist the nurturing and survival of the fetus. Biochemical parameters reflect these adaptive changes and are clearly distinct from the non-pregnant state. The woman's renal function, carbohydrate and protein metabolism, and particularly the hormonal pattern are affected. It is critical to appreciate both normal and abnormal changes as laboratory results can influence the management of both mother and child.

Renal function

During pregnancy the serum sodium is about 3–5 mmol/L lower than normal because of an increase in intravascular volume and the resetting of the osmostat. Cardiac output and renal blood flow are also increased. This leads to an increased glomerular filtration rate (GFR) with resultant decrease in concentrations of serum urea, creatinine and uric acid (Table 1).

In most cases, renal function during pregnancy can be adequately assessed by the serum urea and creatinine. If required, the GFR can be calculated using the Cockcroft-Gault or Method of Disease Renal Diet formulae[1], but it is necessary to take into account the pregnant state specifically. The GFR can also be calculated using urinary volume, urinary and serum creatinine. Radioactive studies of urinary excretion are clearly not appropriate.

The renal tubular threshold is also lowered in pregnancy. This results in an increased excretion of uric acid, amino acids and glucose. Urinary testing for glycosuria can therefore be misleading. Similarly, urinary testing to assess metabolic changes should not be used during pregnancy and is best delayed well into the post-partum period. The best practical uses of urine testing during pregnancy are to diagnose pregnancy itself, to detect asymptomatic bacteruria and to warn of imminent pre-eclampsia when protein excretion rises.

Liver function tests

All markers of liver function are generally reduced or low during pregnancy due to the expansion of extracellular fluid. Hence serum albumin, transaminases (AST and ALT) and total bilirubin are low compared with the non-pregnant state. The only exception is serum alkaline phosphatase (ALP) which is elevated due to ALP of placental origin.

Causes of abnormal liver function tests specific to pregnancy include intrahepatic cholestasis of pregnancy, pre-eclampsia, haemolysis-elevated liver enzymes-low platelets (HELLP) and rarely acute fatty liver of pregnancy (Table 1). All of these can cause significant fetal and maternal morbidity and mortality. Newly acquired hepatitides during pregnancy and adverse drug reactions should also be considered when assessing abnormal liver function tests.

Calcium metabolism

During pregnancy, serum total calcium, phosphate and magnesium tend to be low due to the expanded intravascular space. Concentrations of calcium are also affected by the reduced albumin concentration. However, results all remain within the reference range. If there is any doubt regarding the calcium result measure the ionized calcium concentration as it remains unchanged during normal pregnancy despite changes in vascular volume and binding proteins. The concentration of serum parathyroid hormone tends to be 50% lower in pregnancy, despite the increased urinary excretion of calcium as a result of the increased GFR.[2] Although primary hyperparathyroidism is rare, it remains the commonest cause of hypercalcaemia during pregnancy. However, differentiating it biochemically from familial hypocalciuria hypercalcaemia (which has non-surgical management) is difficult and evaluation at a specialist endocrinology clinic is recommended.

Table 1

Normal reference ranges and their interpretation during pregnancy *

Analytes	Normal (non-pregnant)	Pregnancy	Abnormalities and possible interpretations
Haemoglobin (g/dL)	11.5–16.5	11.0–15.0	Abnormal results need to be considered in conjunction with the patient's clinical state
White cell count (x 10^6 per mL)	4.0–11.0	Unchanged	
Platelets (x 10^6 per mL)	150–450	Unchanged	
Sodium (mmol/L)	135–145	132–140	Abnormal results need to be considered in conjunction with the patient's clinical state
Potassium (mmol/L)	3.5–5.5	3.2–4.6	
Urea (mmol/L)	2.5–6.8	1.0–3.8	↑ in: dehydration hyperemesis gravidarum late stages of pre-eclampsia renal impairment
Creatinine (mmol/L)	0.06–0.1	0.04–0.08	↑ in: renal impairment late stages of pre-eclampsia
Fasting glucose (mmol/L)	3.0–5.4	3.0–5.0	↑ in: gestational diabetes mellitus (refer to reference 3 for diagnostic criteria)
Total calcium (mmol/L)	2.2–2.60	2.0–2.40	↑ in: primary hyperparathyroidism
Ionized calcium (mmol/L)	1.16–1.30	1.16–1.30	
Magnesium (mmol/L)	0.6–1.0	0.6–0.8	↓ in: vomiting hyperemesis gravidarum
Albumin (g/L)	33–41	24–31	↓ in: malnutrition recurrent vomiting hyperemesis gravidarum
Bilirubin (micromol/L)	3–22	3–14	↑ in: intrahepatic cholestasis of pregnancy HELLP late stages of pre-eclampsia acute fatty liver viral hepatitides
Alanine aminotransferase (U/L)	1–40	1–30	↑ in: intrahepatic cholestasis of pregnancy HELLP late stages of pre-eclampsia acute fatty liver viral hepatitides
Aspartate aminotransferase (U/L)	1–30	1–21	↑ in: intrahepatic cholestasis of pregnancy HELLP late stages of pre-eclampsia acute fatty liver viral hepatitides
Alkaline phosphatase (U/L)	25–100	125–250	↑ in: metabolic bone disorders but placental serum alkaline phosphatase needs to be excluded

Adapted from reference 7

↑ increased concentration

↓ decreased concentration

HELLP Haemolysis-Elevated Liver enzymes-Low Platelets

* Each laboratory, where practicable, should develop its own reference ranges for pregnant women. Care should be exercised in comparing results from different laboratories due to differences in assay methodologies.

Carbohydrate metabolism and gestational diabetes mellitus

The concentration of fasting glucose is reduced during pregnancy because of increased substrate utilisation (Table 1). With the increasing incidence of obesity, there will be an increased prevalence of gestational diabetes and type 2 diabetes developing during pregnancy. It is therefore prudent to be familiar with the diagnostic criteria.[3] It is essential to screen for gestational diabetes at 26–28 weeks of gestation so that the correct interpretation can be made. The test is positive if the plasma glucose concentration is 7.8 mmol/L or more one hour after a 50 g glucose load.[3]

Hormonal changes

Pregnancy causes a remarkable number of hormonal changes that continue to evolve throughout the gestational period. This makes the interpretation of biochemical and hormonal results a challenging task. The changes are a continuation of the luteal phase of the menstrual cycle. Once pregnancy has occurred, concentrations of progesterone and oestrogen continue to rise suppressing the secretion of luteinising hormone and follicle stimulating hormone. However, these changes are non-specific and should not be used to confirm pregnancy.

To confirm pregnancy, serum human chorionic gonadotrophin (HCG) is the test of choice. The concentration of HCG is likely to be elevated by trophoblastic activity as early as day eight after implantation. Concentrations peak at approximately 10 weeks and then decline to plateau out at a lower level.

Thyroid function

Thyroid function tests are not uncommonly ordered during pregnancy and interpreting the results is challenging. Physiologically, the concentration of thyroid stimulating hormone (TSH) normally decreases during the first trimester of pregnancy during which there is maximal cross-stimulation of the TSH receptor by HCG. The TSH concentration then returns to its pre-pregnancy level in the second trimester and then rises slightly in the third. However, most of the changes still occur within the normal non-pregnant range. Serum free tri- and tetra-iodothyronine concentrations essentially remain unchanged during pregnancy but total concentrations, which include both free and protein-bound fractions, are significantly elevated due to increased circulating binding globulins.[4] Clinical indicators are usually confounding due to symptoms of pregnancy that can mimic thyrotoxicosis such as nausea, vomiting, heat intolerance, fatigue, anxiety and palpitations. The presence of a goitre, especially in patients with a borderline iodine deficiency, can further confound the diagnosis.

Graves' disease is the commonest cause of true thyrotoxicosis in pregnancy. Where there is prolonged and intractable nausea and vomiting, Graves' disease should be distinguished from hyperemesis gravidarum of pregnancy and transient hyperthyroxinaemia of pregnancy. It is important that they are distinguished from Graves' disease as the prognoses and management are distinctly different (Table 2). Hyperemesis gravidarum and transient hyperthyroxinaemia of pregnancy are often self-limiting and can be treated expectantly with general support and/or beta blockade.[5] Graves' disease needs to be rigorously controlled in order to optimise both fetal and maternal outcome.[4]

Haematology

In pregnancy, there is a gradual increase in circulating blood volume of up to 1.5 L by the third trimester. As there is a relatively smaller increase in red cell mass there is a decrease in haematocrit and haemoglobin concentrations. The white blood cell and platelet concentrations remain essentially stable throughout (Table 1).[6]

Conclusion

Pregnancy results in many changes to laboratory tests which can be misinterpreted as abnormal. In general, most of the analytes have lower concentrations than in the non-pregnant

Table 2

Distinguishing hyperemesis gravidarum and thyrotoxicosis during pregnancy

	Reference range in pregnancy	Graves' disease	Hyperemesis gravidarum
Thyroid stimulating hormone (IU/L)	0.1–4.0	<0.05	<0.05
Free tetra-iodothyronine (pmol/L)*	10.0–25.0	↑↑↑	↑ to ↑↑
Free tri-iodothyronine (pmol/L)*	3.5–6.0	↑ to ↑↑↑	↑ to ↑↑
Human chorionic gonadotrophin	Normal* for gestational age	Normal* for gestational age	↑↑↑ for gestational age
Thyroid stimulating immunoglobulin	Absent	Present	Absent
Thyroid – myeloperoxidase antibodies	Absent or present in low titre	Absent	Absent or low

↑ increase

* Reference ranges often vary between laboratories

state due to increased intravascular volume while the free active fractions, such as ionized calcium, remain unchanged. It is uncommon for a particular analyte to become elevated and thus this is a useful pointer to recognising abnormal laboratory results during pregnancy. When there are clinically discrepant results, it is prudent to seek further advice from the laboratory.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false
(answers on page 107)

7. An increased alkaline phosphatase concentration during pregnancy is abnormal.
8. Glucose excretion is reduced during pregnancy.

Book review

Powerful medicines: the benefits, risks and costs of prescription drugs. Avorn J.

New York: Alfred A. Knopf; 2004. 448 pages. Price approx. $57

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Reading this book is like sitting on the side of a hill watching a faulty train full of happy passengers hurtling towards inevitable catastrophe and being powerless to stop it happening. In fact it's like watching wreck after wreck take place. In these cases the trains are manufactured by the pharmaceutical industry, the passengers are the trusting patients and the drivers are the prescribers who appear blind to the possibility that there could be any danger ahead. The controllers and signallers are the regulatory authorities who may be in the pay of the train's manufacturers or dominated by politicians.

The book starts with examples of recent drug catastrophes. It lays out how, particularly in the USA, the reach of the pharmaceutical industry is everywhere. The authorities, who should be the guardians of drug safety, are subject to a Congress and Senators in the pay of the industry and they are guided by professional experts who should be objective, but instead are recipients of payments and other inducements to support products and launder data. Although we all suspect this to be the case, the true extent of it is almost beyond comprehension.

The book is a very balanced text as would be expected when the author is one of the world's foremost pharmacoepidemiologists. It is not all anti-drug or anti-industry, there are sections on benefits as well as risks and costs. There are sections on policy and on how information about drugs is collected and used. There is an excellent discussion about the choices society has to make about how to get the best value from health dollars.

The book has, of course, a heavy focus on the USA. While this may make it of less interest to readers outside that country, there are many similarities with events here that readers will recognise. For example, the infiltration of the research agenda by the pharmaceutical industry as public research funds become more scarce, and the hijacking of postgraduate education in the same way. We also have medical experts, 'key opinion leaders', who have been subtly bought by the industry.

My one criticism is the use of American trade names even though generic names are usually, but inconsistently, given. Although some generic names are cumbersome and not easily recognised, the international reader will not recognise many of the American names.

The book makes complex topics easily comprehensible. What makes the book so readable, beyond the voyeuristic fascination of watching tragedy after tragedy unfold, is Avorn's sharp humour. For example, '... anti-Parkinson drugs are a rough crowd to invite across your blood-brain barrier if you don't have to'.

Jerry Avorn is a world expert and also a brave crusader. Anyone who ever prescribes, dispenses or takes a medication should pause before they do so to read this book. They may make a different choice as a result.