Changes in biochemical tests in pregnancy and their clinical significance

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Abstract

Interpretation of laboratory investigations relies on reference intervals. Physiological changes in pregnancy may result in significant changes in normal values for many biochemical assays, and as such results may be misinterpreted as abnormal or mask a pathological state.

The aims of this review are as follows:

1. To review the major physiological changes in biochemical tests in normal pregnancy.
2. To outline where these physiological changes are important in interpreting laboratory investigations in pregnancy.
3. To document the most common causes of abnormalities in biochemical tests in pregnancy, as well as important pregnancy-specific causes.

Keywords

Endocrinology, biochemistry, pregnancy reference intervals

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Several studies have documented the physiological changes that occur in many biochemical laboratory tests in normal pregnancy.^{1–8}

There is significant variability between laboratories depending on the method of testing, the assay used and population factors. Wherever possible clinicians should use a reference interval specific to the laboratory that has performed the test.

Users and laboratories should consider how to reliably code gestational age and work towards developing validated laboratory-specific reference intervals and decision thresholds in their population.

Renal

Early in first trimester renal plasma flow and glomerular filtration rate each rise by approximately 60% above preconception values, resulting in a fall in serum creatinine (se Cr), urea and urate by 25%. Measures of renal function then remain steady throughout pregnancy. In the third trimester renal plasma flow declines to preconception values and se Cr trends upwards towards pre-pregnancy levels.

It is important to recognise that se Cr levels which would be in the normal interval outside of pregnancy may represent renal dysfunction during pregnancy. It is also important to anticipate a rise in se Cr from the second to the third trimester especially in women with pre-conception renal dysfunction. This rise in se Cr improves postpartum but not entirely to baseline.⁹

The pregnancy-specific variation in serum urate may have implications if part of the diagnostic strategy in PET.

No estimation formulae for eGFR have been validated in a pregnant population so should not be used.

Urinary protein and albumin excretion rise during pregnancy especially from 20 weeks' gestation. This has commonly been attributed to the increase in GFR although the timing is not in parallel.⁹ Another potential cause is selective alterations in glomerular charge. The amount of proteinuria may increase significantly during

pregnancy in women with preconception proteinuria, making diagnosis of superimposed preeclampsia (PET) difficult.

PET/Hemolysis, Elevated Liver enzymes and Low Platelet count (HELLP) syndrome account for 60–80% of cases of acute kidney injury (AKI) during pregnancy in developed countries.¹⁰ Other important causes of AKI include placental abruption, sepsis, postpartum haemorrhage, renal obstruction, acute fatty liver of pregnancy (AFLP), haemolytic-uraemic syndrome/thrombotic thrombocytopenic purpura and non-steroidal anti-inflammatory drug use postpartum.

In developing countries sepsis accounts for approximately 40% of cases of AKI.

Twenty-four hour urine protein estimations may be inaccurate due to under- or over-collection. Errors in timing and retention may also occur due to large volumes of urine within dilated collecting systems.¹¹ Urine protein:Cr ratios on spot collections correlate well with 24 h urine protein estimations and the time of day of collection does not impact on accuracy.^{12,13}

Plasma osmolality and sodium

There is a 3 l gain of water in pregnancy which contributes to significant haemodilution of many electrolytes. Water balance is controlled by thirst and the secretion of ADH, which are regulated primarily by serum osmolality. In pregnancy the osmotic threshold for ADH release and thirst stimulus is reset down,^{14,15} a process which has been interpreted to result from a baroreceptor stimulus from arterial

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underfilling overwhelming the osmostat.¹⁶ Vasopressinase is released by placental trophoblasts in concentrations proportional to placental weight, so activity is higher in the third trimester or in multiple pregnancies. Vasopressinase causes degradation of ADH and might be expected to thus cause some tempering of the effects of the reset osmostat towards the end of the pregnancy, although an increase in osmolality in the later stages of pregnancy are atypical.

Serum osmolality falls by 10 mOsm/kg early in pregnancy reaching a nadir at the end of first trimester that is maintained until the end of pregnancy. In the absence of marked hyperglycaemia or renal failure, serum sodium (Na) levels in pregnancy parallel serum osmolality. Na falls by 3–6 mmol/l.^{3–8} The most common cause of severe hyponatraemia in pregnancy is PET. Razavi et al.¹⁷ found hyponatraemia complicated 9.7% of pregnancies with PET. Hyponatraemia is associated with a picture of syndrome of inappropriate antidiuretic hormone (SIADH) release with elevated urine Na and inappropriately high urine osmolality, although SIADH implies the absence of hypervolemia so strictly cannot be diagnosed in pregnancy. Hyponatraemia is more common with earlier onset PET, where significant oedema is present, with twin pregnancies and with older women. Possible explanations include insufficient vasopressinase produced by a defective placenta, or excess ADH or oxytocin produced by placenta or myometrium due to premature contractions under the influence of ovarian steroids. Hyponatraemia with a picture of SIADH may also be seen with prolonged labour, post-caesarean section and with the use of non-steroidal anti-inflammatory drugs for analgesia postpartum.^{18–20} Severe hyponatraemia has also been reported with oxytocin infusions for induction of labour, primary polydipsia and hyperemesis gravidarum.^{21–24}

Glucocorticoid deficiency and/or hypothyroidism related to Sheehan's syndrome and lymphocytic hypophysitis should be excluded in women with peripartum hyponatraemia.²⁵

Hyponatraemia is rare in pregnancy. Gestational diabetes insipidus may occur, usually in the second or third trimesters, due to excess placental vasopressinase activity.²⁶ Diabetes insipidus may also occur with AFLP and hepatic injury with PET, as a result of reduced hepatic degradation of vasopressinase.²⁷ Rarely diabetes insipidus may be unmasked in pregnancy in women with reduced vasopressin production due to previous neurosurgery or head trauma, or acutely in the setting of pituitary apoplexy.²⁸

The water deprivation test is considered unsafe in pregnancy. Diagnosis of diabetes insipidus requires assessment of basal urine and plasma osmolality, and response to desmopressin.²⁹

Renin–angiotensin–aldosterone (RAA) axis

Pregnancy is a state of hyperreninaemic hyperaldosteronism. Vascular underfilling seen by the kidneys results in stimulation of the RAA system. Renin is also produced by the ovaries and uteroplacental unit. Oestrogens stimulate the synthesis of angiotensinogen which result in proportionally higher levels of aldosterone compared with renin. Progesterone is an antagonist of aldosterone, and thus the effects of increased aldosterone are tempered during pregnancy.

Plasma aldosterone concentrations increase approximately 3–8-fold compared with non-pregnant values, plateauing in third trimester. Similarly 24 h urine aldosterone excretion at term is approximately eight-fold higher than pre-pregnancy.³⁰ Plasma renin activity (PRA) increases approximately four-fold by eight weeks' gestation and seven-fold at term. As a result aldosterone:renin ratios (ARRs) may fall in pregnancy affecting the diagnosis of primary aldosteronism.³¹

The hormonal changes in the RAA result in false negative testing during pregnancy in 40% of women with known primary aldosteronism.³² Elevated ARR together with PRA less than 54 mU/l is strongly suggestive of primary aldosteronism in pregnancy.³³ Dynamic tests to

confirm primary aldosteronism are generally not performed during pregnancy because of concerns regarding salt and volume loading, though values for well pregnant women following saline infusion have been published.³⁴ Until pregnancy-specific reference intervals for direct renin concentration are available, PRA is the preferred method in determination of ARR, to minimise false positives.³⁵

Betamethasone suppresses maternal aldosterone by approximately 50% for two days after administration.³⁶

PRA is not a useful guide regarding mineralocorticoid replacement with Addison's disease or congenital adrenal hyperplasia in pregnancy.³⁷

Labetalol does not affect PRA.³⁸

Potassium

Despite the large increase in aldosterone during pregnancy, potassium excretion is tempered by oestrogen and progesterone increasing sodium reabsorption in the proximal nephron and progesterone acting as a mineralocorticoid antagonist in the distal nephron.³⁹ There continues to be conjecture concerning the mechanism for fine control of potassium homeostasis during pregnancy.

Serum potassium (K) is approximately 0.3 mmol/l lower in the third trimester compared with pre-pregnancy.^{3–4}

There is a net retention of potassium during pregnancy, but it is unclear whether this is related to renal retention or gastrointestinal retention. Two studies described a fall in 24 h urine K excretion in pregnancy,^{39,40} but this finding has contrasted with others reporting no change in urinary potassium excretion between the follicular phase and nine weeks' gestation⁴¹ or when comparing second and third trimesters.^{10,42}

The potential decrement in urine K excretion in pregnancy must be taken into account in differentiating whether hypokalaemia is due to gastrointestinal or renal losses of potassium.

The most common cause of hypokalaemia in pregnancy is vomiting with morning sickness/hyperemesis.⁴³ Gitelman syndrome is the second most commonly reported cause of hypokalaemia in the literature and may be unmasked in pregnancy.⁴⁴ Diagnosis of Gitelman and Bartter syndromes is based on genetic testing, as normal pregnancy is associated with hyperreninaemic hyperaldosteronism, and differentiation between the two disorders based on urinary calcium excretion may be affected by the physiologic rise in urine calcium in pregnancy. Unusual causes of hypokalaemia in pregnancy include pica/geophagia, excessive ingestion of caffeine or carbonated beverages, hyperventilation, renal tubular acidosis and following administration of betamethasone.^{45–48} A mineralocorticoid receptor mutation resulting in hypokalaemia from agonist action of progesterone and cortisol metabolites may be unmasked in pregnancy.^{49,50} Hypokalaemia with primary aldosteronism may resolve in pregnancy due to the anti-mineralocorticoid effect of progesterone. Primary aldosteronism should be considered where there is hypertension and hypokalaemia worsening postpartum when progesterone levels drop.⁵¹

Importantly, there is an increased predilection for rhabdomyolysis and paralysis with hypokalaemia in pregnancy.^{52–54}

Hyperkalaemia is rare in pregnancy. Pregnancy-specific causes include case reports of hyperkalaemia due to labetalol therapy, following magnesium sulphate infusion, and type 4 renal tubular acidosis related to diabetic kidney disease which may worsen through pregnancy.^{55–58}

Liver enzymes

Pregnancy is associated with mild falls in alanine aminotransferase, aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT) and bilirubin. This may be related to lower intake of

hepatotoxic drugs and alcohol in pregnancy.⁵⁹ Pregnancy is also associated with a fall in serum albumin beyond what would be expected from the increase in circulating volume, and despite a 50% increase in albumin synthesis in the liver, and it has been hypothesised that there might be albumin catabolism to improve delivery of amino acids to the fetus.³ Some authors have reported that lactate dehydrogenase (LDH) may rise from in first trimester, normal values in third trimester being up to double values pre-pregnancy.⁴ Other authors report no change in LDH.⁵⁹ Levels of cholic acid and deoxycholic acid are unchanged during pregnancy^{60,61} though levels of chenodeoxycholic acid increase significantly postpartum.⁶¹

Levels of alkaline phosphatase (ALP) rise due to production of the placental isoenzyme, as well as a significant increase in bone isoenzyme in third trimester. Prothrombin time falls progressively from the second trimester such that values are approximately 10–20% lower than preconception values in the third trimester.⁶² This may be important when considering abnormal hepatic synthetic function with disorders such as AFLP. Serum amylase activity is similar in non-pregnant women and pregnant women in all trimesters of pregnancy. Serum lipase activity is significantly lower in the first trimester but not the later trimesters compared with non-pregnant women.⁶³

Important causes of acutely elevated transaminases in pregnancy include PET (HELLP syndrome), drug reactions, AFLP, viral and autoimmune hepatitis, sepsis and intrahepatic cholestasis of pregnancy. A LDH:AST ratio of greater than 22 may be helpful in distinguishing thrombotic thrombocytopenic purpura from HELLP syndrome.⁶⁴

Raised serum bile acids are the best indicator of intrahepatic cholestasis, although transaminases are elevated in about half of cases, GGT in about a third, and bilirubin may be modestly increased in up to 30%.⁶⁵

An acute rise in ALP may signify placental damage or infarction.⁶⁶ Elevated placental ALP may also be seen with antiphospholipid syndrome.⁶⁷ If required, distinction of placental ALP from liver or bone isoenzyme may be made by serum ALP electrophoresis.

Possible physiological changes in LDH may be relevant where LDH is being used as a tumour marker.

The most common cause of hypoalbuminaemia in pregnancy is PET.⁶⁸ Albumin levels are on average 15% lower in PET than in healthy pregnancy.⁶⁹

Hyperemesis gravidarum has been reported to be associated with significantly elevated levels of lipase and amylase in the absence of clinical pancreatitis.⁷⁰

Gas exchange/arterial blood gas

An increase in minute ventilation driven by progesterone increases oxygenation despite the 20% increase in oxygen consumption in pregnancy, reduces carbon dioxide and results in a respiratory alkalosis which is fully compensated by renal bicarbonate excretion.

Bicarbonate levels are 25% lower in pregnancy.²

There is a difference between sitting and supine arterial oxygen concentration in the latter half of pregnancy, and by term supine PaO₂ is 7 mmHg lower than sitting PaO₂.⁷¹ The mechanism for this is not clear.

Even mild reductions in PaO₂ are likely to signify underlying pathology. Similarly a PaCO₂ in the normal non-pregnant range may represent respiratory fatigue in a pregnant woman with an acute exacerbation of asthma.

The peripartum period is often the first time women have pulse oximetry performed. Clinicians need to be aware of the rare possibility of variant haemoglobins where there are unexpectedly low pulse oximetry saturations with normal PaO₂ on arterial blood analysis.⁷²

Diabetic ketoacidosis may occur more rapidly and at lower blood glucose levels in pregnancy related to the reduced serum bicarbonate and thus reduced buffering capacity.⁷³

Starvation ketoacidosis may occur after periods of fasting less than 16 hours in the second and third trimester due to insulin resistance and reduced serum bicarbonate.⁷⁴

Calcium/bone

A slight fall in unadjusted calcium, magnesium (Mg) and phosphate occurs in pregnancy. Corrected calcium results may be falsely elevated due to changes in albumin. Ionised calcium, which does not change in pregnancy, should be measured instead. Parathyroid hormone (PTH) levels fall by approximately 50% in the second and third trimester as levels of parathyroid hormone-related peptide (PTHrP) rise, but there remains a relationship between PTH and 25-vitamin D in pregnancy.⁷⁵ PTHrP is the major hormonal mediator of calcium homeostasis in pregnancy, is produced mainly by the placenta and peaks in the third trimester,^{76,77} and mimics the effect of PTH on kidneys and bone. 25 hydroxy-vitamin D levels remain unchanged, while levels of 1,25 (OH)₂ vitamin D rise due to the effect of PTHrP and oestrogen stimulating 1-alpha hydroxylase.

Urine calcium excretion increases up to 2–3-fold during pregnancy commencing at 12 weeks' gestation due to increased calcium absorption and increased GFR.

Serum Mg declines such that levels in third trimester are 30% lower than preconception.^{78–82} Similarly ionised and red blood cell Mg, and intracellular free Mg in brain and muscle are lower in pregnancy than in non-pregnant controls when measured by nuclear magnetic resonance spectroscopy.^{83,84}

Urine Mg excretion rises by approximately 25% during pregnancy.^{85,86}

Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcaemia in pregnancy,⁸⁷ and surgical intervention in the second trimester has been advocated with serum calcium levels above 2.75–2.85 mmol/l.⁷⁶ Other important causes include milk-alkali syndrome (triad of hypercalcaemia, alkalosis and AKI), familial hypocalciuric hypercalcaemia (FHH) and PTHrP-mediated hypercalcaemia. The clinical symptoms of PTH-related hypercalcaemia may be masked by other physiological changes in pregnancy, and the diagnosis might be missed by falsely normal total calcium levels in the absence of measurement of ionised calcium levels, with physiologically lowered PTH levels.

The rise in urine calcium may cause difficulty in differentiating FHH and PHPT and thus risk unnecessary neck exploration. More than 100 mutations in the calcium-sensing receptor have been identified; however, a mutation is only detected in two-thirds of cases of FHH.⁸⁸ Measuring calcium in relatives may be a more rapid and reliable way of differentiating between FHH and PHPT in pregnancy.⁸⁹ In addition, the physiologic hypercalciuria of pregnancy may result in difficulty in establishing the diagnosis of Gitelman syndrome without genetic testing. Hypercalciuria of pregnancy increases the risk of renal calculi. Falling urine calcium as early as first trimester may predict the later development of PET.^{90,91} The decrease in urine calcium is due to a fall in GFR rather than increased tubular reabsorption.

Hypocalciuria may also be seen in pregnant women with vitamin D deficiency.

Hypocalcaemia commonly occurs with magnesium sulphate infusion. Hypocalcaemia may also occur with vitamin D deficiency and hypomagnesaemia.

Important causes of hypomagnesaemia in pregnancy include poorly-controlled diabetes mellitus, Gitelman/Bartter syndromes, congenital tubular defects, alcohol, PET and previous jejunio-ileal bypass surgery.⁹² A very rare cause of severe hypomagnesaemia and diabetes mellitus is mutations in the hepatocyte nuclear factor 1 β or 4 β genes.⁹³

Cardiac markers

Levels of troponin I (TnI) are unchanged in healthy pregnancy and are not affected by labour, anaesthesia, or caesarean section.^{94–99} Most studies have shown that brain natriuretic peptide (BNP) levels remain unchanged compared with preconception levels in normotensive women throughout pregnancy.^{100–103} One longitudinal study of 29 healthy pregnant women showed no significant differences between BNP levels throughout trimesters and in the postpartum period, though pregnant BNP levels were approximately twice as high as in non-pregnant controls.¹⁰⁰ In healthy women BNP levels rose approximately 2–3-fold in the first 48 h postpartum returning to baseline 6–12 weeks' postpartum. The rise in BNP correlated with an increase in left atrial and left ventricular volume on echocardiography; however, cardiac output was not increased. It is postulated this may relate to uteroplacental transfusion, release of vena caval obstruction and mobilisation of extravascular fluid. Mild elevation of BNP postpartum may therefore represent a physiologic change and not evidence of cardiac pathology. Chronic hypertension, gestational hypertension and PET are all associated with elevated BNP.^{102–104} In individuals with PET, elevation of BNP may persist for 3–6 months' postpartum.¹⁰⁵

Studies as to whether PET is associated with a rise in cTnI have revealed inconsistent results.¹⁰⁶

Five studies found PET was associated with significantly higher values for TnI than uncomplicated pregnancy.^{107–110}

Four authors found no difference in levels of TnI in normotensive pregnancy and PET.^{111–114} Bozkurt et al.¹¹¹ found that while TnI levels were not increased with PET, levels were higher in women with eclampsia. Two of these studies specifically investigated women with severe PET finding no significant difference in TnI with normotensive women.^{112,113}

Two studies showed normal troponin T (TnT) levels in healthy pregnancy.^{110,115}

No data have been published regarding levels of high sensitivity troponin in pregnancy, but studies examining normal reference intervals would be useful.

Women of child-bearing age are at low risk of atheromatous coronary artery disease, although ischaemic heart disease is becoming increasingly common in pregnancy. In pregnant women with elevated troponin but otherwise inconclusive evidence for myocardial ischaemia, other diagnoses such as pulmonary embolism, obstructive sleep apnoea, coronary artery dissection, illicit drug use (cocaine, amphetamines and heroin) and false elevation of troponin due to heterophile antibodies should be considered.

Thyroid

Human chorionic gonadotropin (hCG) is structurally similar to thyroid stimulating hormone (TSH) and has a direct stimulating effect on the TSH receptor. hCG levels peak at the end of first trimester resulting in a transient increase in free thyroxine (fT4) and a fall in TSH levels. Hyperemesis gravidarum is often associated with high hCG levels that can cause transient and self-resolving hyperthyroidism.¹¹⁶

Thyroxine-binding globulin increases 2–3 times compared with pre-pregnancy by 20 weeks' gestation, as a result of increased hepatic production induced by oestrogen and reduced clearance.¹¹⁷ As a result the dose of thyroxine should be increased by approximately 30% in women on thyroxine supplementation early in pregnancy.

Maternal iodine requirements increase in pregnancy due to transfer to the feto-placental unit and increased urine excretion.

There are large differences in reference intervals for thyroid function between different populations of pregnant women due to variations in assays as well as population-specific factors such as ethnicity,

maternal iodine status and body mass index. It is recommended that institutions calculate their own trimester- and method-specific reference intervals rather than relying on fixed universal cut-off concentrations. Treatment targets may be distinct from reference intervals, and a large body of literature continues to debate treatment targets for thyroid function parameters during pregnancy.^{118–120}

Some suggest for those women on long-term thyroxine supplementation aiming for TSH in lower half of non-pregnant reference range, particularly from weeks 4 to 11 when the fetal brain is developing.

Anti-thyroid peroxidase and/or anti-thyroglobulin antibodies are found in 15–20% of Australian women at 10–13 weeks' gestation and influence the TSH treatment target.¹²¹ TSH levels in antibody-positive pregnant women tend to be significantly higher and they should not be included in establishing reference interval intervals.¹²² Antibody levels tend to fall during pregnancy.

Common causes of elevated TSH in pregnancy include failure to increase thyroxine supplementation in hypothyroid women, poor medication adherence, interference with absorption due to concomitant ingestion of calcium- or iron-containing foods or supplements, coexistent coeliac disease (present in 3% of women with autoimmune thyroiditis), iodine deficiency or excess, women with nephrotic range proteinuria (due to urinary loss of thyroxine).^{123–127} In women presenting with newly diagnosed hypothyroidism within 12 months of delivery of a previous baby, the possibility of undiagnosed persistent postpartum thyroiditis should be considered.

The most common cause of low TSH in first trimester of pregnancy is due to hCG stimulation. Ten to twenty per cent of normal women have transiently low or undetectable TSH levels as a result, usually with normal fT4 and fT3, though these may be mildly elevated. hCG-mediated thyrotoxicosis may be differentiated from Graves' disease by the absence of TSH receptor antibodies, absence of increased colour flow Doppler on ultrasound and by measurement of erythrocyte zinc levels.^{128–130} Severe thyrotoxicosis may occur with gestational trophoblastic disease.

Graves' disease is the second most common cause of thyrotoxicosis in pregnancy.

Ingestion of large quantities of biotin may cause a picture suggestive of Graves' disease with elevated fT4, elevated fT3, elevated TSH receptor antibodies and low TSH due to interference with immunoassays.¹³¹

Maternal contact with fetal tissue epitopes during amniocentesis may trigger thyroid hormone antibodies and cause false elevation in fT4 and fT3.¹³²

Heterophile antibodies commonly complicate interpretation of thyroid function tests and should be suspected if there is a discrepancy between thyroid function and clinical status. There are no known pregnancy-specific heterophile antibodies.

Hypothalamic–pituitary–adrenal (HPA) axis

Total plasma cortisol, 24 hour urine free cortisol (24 h UFC), nocturnal salivary cortisol (NSC) and cortisol-binding globulin (CBG) levels progressively rise three-fold during pregnancy.

Placental production of corticotropin-releasing hormone and adrenocorticotrophic hormone (ACTH) results in a three-fold rise in these hormones, which decrease within 2 hours of delivery.¹³³

Plasma free cortisol increases 1.6-fold by the third trimester.¹³⁴ During the final weeks of pregnancy there is a substantial fall in CBG with a corresponding further rise in plasma free cortisol.

The diurnal rhythm of ACTH and cortisol is preserved.⁸

The HPA axis sensitivity to exogenous glucocorticoids is lost, thus the dexamethasone suppression test is not useful for the diagnosis of Cushing's syndrome (CS).¹³⁵ A 24 h UFC more than three times the upper end of the normal non-pregnant interval is strongly suggestive of CS. An elevated NSC is also useful in the diagnosis of CS.¹³⁶

ACTH levels cannot be used to differentiate between pituitary and adrenal causes of CS, as ACTH levels are not suppressed in half of adrenal CS, whereas some pregnant women with pituitary Cushing's disease have been reported to have suppressed ACTH.^{137–138}

A random morning serum cortisol measured by liquid chromatography–tandem mass spectrometry of less than 300 nmol/l in first trimester, less than 450 nmol/l in second trimester and less than 600 nmol/l in third trimester should raise a clinical suspicion of adrenal insufficiency (AI).^{134,139} Trimester-specific values have been proposed for use with synacthen stimulation tests for diagnosis of AI (700, 800, 900 nmol/l, respectively, but adjustment to local assays is advised); however, stimulated salivary free cortisol values may be a more consistent measure of synacthen-stimulated adrenal function than serum cortisol.¹³⁹ Metyrapone may be used in pregnancy; however, there are no established values for the diagnosis of HPA axis insufficiency.

The aetiology of CS is significantly different in the pregnant compared with the non-pregnant population.¹⁴⁰ Approximately 30% of cases of CS reported in pregnancy have been due to Cushing's disease, 42% due to adrenal adenoma, 14% due to adrenal carcinoma, 10% due to pregnancy-induced CS as a result of aberrant LH/hCG receptor expression and 4% due to ectopic ACTH syndrome.

The most common cause of HPA axis insufficiency in pregnancy is following the use of betamethasone, where suppression of maternal cortisol may be prolonged.¹⁴¹ Uncommon causes of HPA axis insufficiency include lymphocytic hypophysitis, Sheehan syndrome and the use of exogenous glucocorticoids including metered aerosols and skin lightening creams containing highly potent corticosteroids.

Primary AI in pregnancy may occur with bilateral adrenal haemorrhage with antiphospholipid syndrome.¹⁴²

Growth hormone (GH)/insulin-like growth factor-I (IGF-I)

The main source of GH in first trimester is from the maternal pituitary.¹⁴³ Placental GH becomes the dominant source of GH from 15 weeks' gestation, increasing exponentially until 37 weeks' gestation, with pituitary GH dropping to undetectable levels. Most assays do not distinguish between pituitary and placental GH. These normal changes limit the usefulness of regular monitoring of levels during pregnancy.

Placental GH does not suppress after a glucose load so the oral glucose tolerance test is difficult to interpret.¹⁴⁴

IGF-I has a modest fall in the first trimester, increasing during the second half of pregnancy peaking at two times the upper end of the normal non-pregnant reference interval at 37 weeks' gestation.¹⁴⁵

In pregnant patients with acromegaly, IGF-I levels usually fall compared with preconception levels, possibly due to oestrogen-induced increases in GH-binding protein and a state of GH resistance, or related to pregnancy-specific assay interference.¹⁴⁶

Prolactin

Prolactin increases approximately 10-fold in first trimester and may be greater than 20-fold of the preconception levels by term. There is therefore no value in monitoring prolactin levels in pregnancy except where doing so to monitor medication adherence in pregnant women receiving dopamine agonists for macroprolactinomas.

Glycaemic control

In non-diabetic pregnant women haemoglobin A1c (HbA1c) levels fall in the second trimester and rise in the third trimester.⁸ Some advocate for the use of HbA1c in screening for impaired glucose tolerance and type 2 diabetes in the first trimester. HbA1c is

significantly higher in women with iron deficiency, and thus may not be useful as an accurate measure of glycaemic control during pregnancy.¹⁴⁷ Fructosamine levels reflect glycaemic control in the preceding 1–3 weeks. Fructosamine levels fall progressively during pregnancy due to the dilutional effect on plasma proteins. Fructosamine is associated with larger intra-individual variability than HbA1c and may be disadvantageous for detecting significant change. Fructosamine levels are lower in the setting of increased protein metabolism (e.g. proteinuria, hyperthyroidism) and are also affected by substances with reducing ability such as bilirubin and ascorbic acid.¹⁴⁸ Glycated albumin (GA) reflects glycaemic control in the previous 2–3 weeks and more accurately reflects postprandial glucose than HbA1c. GA levels fall in the second and third trimester.¹⁴⁷ 1,5-anhydroglucitol (1,5-AG) levels reflect glycaemic control in the previous 24 hours. 1,5-AG levels steadily decrease from 9 weeks' gestation in normal pregnancy because of the reduced renal threshold for glycosuria, and therefore are not an appropriate indicator of diabetic control in pregnancy.¹⁴⁹ Of these above measures of glycaemic control HbA1c is the only one that has been standardised.

GA is a superior predictor of perinatal complications to HbA1c.¹⁵⁰

Pregnancy is a state of insulin resistance, accelerated starvation and reduced buffering capacity due to respiratory alkalosis, especially in the second half of pregnancy.⁷³ Starvation ketoacidosis may occur after brief periods of fasting (greater than 16 hours) even in pregnant women with normal glucose tolerance.¹⁵¹ Ketoacidosis may also be precipitated by the administration of glucocorticoids for fetal lung maturation.¹⁵²

International consensus has not been reached regarding the recommended method and criteria for the diagnosis of GDM. A meta-analysis of prospective cohort studies and control arms of randomised trials found graded linear associations between maternal glucose concentrations and adverse perinatal outcomes with no clear evidence of a threshold effect.¹⁵³ Adoption of the new International Association of Diabetes and Pregnancy Study Groups criteria may result in a considerable increase in the incidence of GDM with an accompanying increase in health costs and requirement for resources. It is unclear as to whether this results in consistent improvements in pregnancy or neonatal outcomes.^{154,155} A recent Cochrane Library review concluded large randomised trials are required to establish the best strategy for diagnosis of GDM.¹⁵⁶ Research investigating the cost-effectiveness of varying glucose thresholds for the diagnosis of GDM on perinatal outcomes is required.

Recommendations for glycaemic targets and timing of glycaemic monitoring in gestational diabetes mellitus vary among different medical societies.¹⁵⁷ This lack of uniformity exists because of a lack of evidence on glucose data and pregnancy outcome.¹⁵⁸ No randomised trial has defined optimal treatment targets. Recommendations for fasting blood glucose targets range between less than 5.0 and 5.3 mmol/l, 1 hour post-meal glucose between less than 7.0 and 7.8 mmol/l, and 2 hour post-meal between less than 6.4 and 6.7 mmol/l. A meta-analysis demonstrated fasting glucose less than 5 mmol/l in third trimester was associated with a reduction in the risk of macrosomia, neonatal hypoglycaemia and maternal PET.¹⁵⁹ A randomised controlled trial comparing pre-prandial and postprandial testing revealed reduced adverse pregnancy outcomes with decision making based upon 1 hour postprandial target glucose of less than 7.8 mmol/l compared with pre-prandial targets of 3.3–5.8 mmol/l.¹⁶⁰ No study to date has evaluated whether monitoring blood glucose 1 or 2 hours post-meal is superior. Tight glucose control may increase the risk of a small for gestational age (SGA) infant. When mean blood glucose was less than 4.8 mmol/l throughout pregnancy there was a 20% incidence of SGA, compared with 11% in a control group.¹⁶¹

Glycaemic targets for women with type 1 diabetes mellitus need to be personalised based upon the individual risk of hypoglycaemia and degree of hypoglycaemic awareness.

Lipids

Total and LDL cholesterol levels double, and triglycerides rise three-fold in pregnancy due to increased hepatic production and reduced activity of lipoprotein lipase. No reference ranges have been established so routine testing should not be performed in pregnancy. Women with underlying hypertriglyceridaemia may develop a severe rise in triglycerides during pregnancy which may lead to chylomicronaemia and pancreatitis.^{162,163}

Lipid levels fall rapidly postpartum and plateau after three months.¹⁶⁴ In women with GDM or PET lipids remain elevated throughout 12 postpartum months.¹⁶⁴

Cholesterol and triglycerides fall more rapidly in women who breastfeed than those who do not establish lactation.¹⁶⁵

Sex hormones

Oestradiol levels progressively rise during pregnancy reaching 100-fold of pre-pregnancy values in third trimester. Similarly there is a progressive marked rise in levels of progesterone and 17-hydroxyprogesterone (17-OHP).¹⁶⁶ The levels of testosterone rise to be approximately five times pre-pregnancy values at term.¹⁶⁷ Sex-hormone-binding globulin levels increase approximately five-fold during pregnancy.¹⁶⁸

Follicle-stimulating hormone and luteinising hormone are low and similar to the follicular phase.

In pregnant women with congenital adrenal hyperplasia, testosterone, androstenedione and 17-OHP should be measured every 2–3 weeks adjusting the glucocorticoid dose to maintain androgen concentrations within normal intervals for the relevant stage of pregnancy.^{169–170}

Iron metabolism

Serum ferritin drops progressively from the first trimester and reaches a nadir by the third trimester of approximately 50%, independent of iron balance.¹⁷¹ Serum ferritin is still the best biomarker for iron status during pregnancy, but a lower cut-off level for iron deficiency should be used.¹⁷¹ Serum transferrin receptor correlates well with the severity of anaemia in pregnancy,¹⁷² but the assay is not widely available. Serum iron levels remain relatively stable. Serum transferrin increases by approximately 10%. Transferrin saturation falls slightly. Transferrin iron-binding capacity increases progressively from first trimester.¹⁷³

Trace elements

Serum ceruloplasmin levels and with it total serum copper progressively rise during pregnancy from the sixth week of gestation such that third trimester serum copper levels are approximately double that of pre-pregnancy levels.^{174–176} This may be important in the diagnosis and monitoring of pregnant women with Wilson's disease. Serum copper levels are significantly lower in the setting of PET than in healthy pregnant women.¹⁷⁷

Zinc binds albumin, and with the reduction in albumin in pregnancy, serum total zinc levels are approximately 15% lower in third trimester than in first trimester.¹⁷⁸ Zinc levels are significantly lower in PET than in healthy pregnant controls. Zinc deficiency in some, but not all studies has been associated with intrapartum haemorrhage, congenital anomalies, intrauterine growth restriction and impaired immunological and neurobehavioural development in the fetus.^{179–182}

Other

Total B12 falls in pregnancy due to reduction in holohaptocorrin. Active B12 (holotranscobalamin) remains unchanged and should be used as guide to B12 deficiency in pregnancy.¹⁸³

Plasma metanephrines are unchanged during pregnancy. Plasma normetadrenaline levels may be elevated up to two-fold in individuals with obstructive sleep apnoea, as well as with antidepressant medications.^{184–186} Levels should be assessed prior to commencement of interfering medications in hypertension in pregnancy.

Serum hCG levels rise significantly in the setting of significant renal dysfunction and cannot be used to diagnose pregnancy.¹⁸⁷

The physiologic rise in alpha feto-protein during pregnancy is relevant where these are being used for screening for hepatocellular carcinoma or germ cell tumours.¹⁸⁸

Similarly Ca-125 may be elevated in the first trimester and postpartum, but it still has utility as a screening tool for ovarian malignancy in the second or third trimesters.^{189,190}

α -1 antitrypsin levels rise steadily throughout pregnancy such that third trimester values are approximately 2.5 times those preconception.¹⁹¹

Most authors state C-reactive protein remains unchanged during pregnancy. Levels, however, rise up to four-fold in the first two days postpartum following normal vaginal delivery,¹⁹² and higher following caesarean section and vacuum extraction.¹⁹³

Fecal calprotectin levels remain unchanged in normal pregnancy, though rise in parallel with disease activity in women with inflammatory bowel disease. C-reactive protein does not rise with disease activity.¹⁹⁴

Conclusion

In conclusion changes in physiology result in many significant alterations in reference intervals for biochemical tests in pregnancy. Awareness of these changes and pregnancy-unique disorders causing laboratory abnormalities is critical in the management of pregnant women. Laboratory-specific reference intervals are desirable for optimal pregnancy care.

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