Review Article

Laboratory tests to monitoring physiological pregnancy

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Abstract: A series of profound physiological changes happen during pregnancy in women body, mainly to facilitate the proper growth and development of the embryo and fetus. These changes include every organ system in the body, causing hormonal and metabolic modifications and plasma volume increase. Laboratory medicine can simultaneously measure several biological constituents' levels and, hence, tests play an essential role in monitoring physiological pregnancy as well as for detecting pathological alteration when present. Further, the assessment of laboratory parameters during pregnancy is considered as a part of the routine examination for pregnant women, and it is included in National and International Antenatal Care (ANC) programs. For this purpose, ANC screening programs usually include complete blood count, blood group and antibody screen as well as urine evaluation and measurement of glycemic conditions. Syphilis, human immunodeficiency virus (HIV) and hepatitis are also usually evaluated to prevent transmission to the newborn. Appropriate pregnancy reference intervals are also needed to help clinicians to avoid interpreting normal results as pathological and to identify abnormal results.

Keywords: Pregnancy; complete blood count; reference intervals; blood groups; gestational diabetes; laboratory tests

Received: 02 December 2019; Accepted: 30 December 2019; Published: 20 January 2020.
doi: 10.21037/jlpm.2019.12.02
View this article at: http://dx.doi.org/10.21037/jlpm.2019.12.02

Introduction

Pregnancy causes profound physiological changes, and, during this period, women's bodies undergo to an adaptation process to accommodate fetus growth. Laboratory medicine covers an essential role in the monitoring of these physiological changes. Indeed, laboratory tests are universally recognized as a meaningful tool for the detection of pathological conditions during pregnancy. Interpretation of laboratory tests should be carefully accounted for physicians for the management of the pregnant mother. Pregnancy-specific (or trimester-specific) reference intervals are often requested to avoid incorrect diagnoses. Furthermore, it should be considered that, when treating a pregnant mother, simultaneous care for both mother and fetus are needed. This because mother and fetus health are intertwined.

Maternal physiological changes during pregnancy

Human average gestation is 40 weeks and is usually divided by physicians into three-time intervals, called trimesters. By convention, the first trimester begins on the first day of the last menses. The last time interval of the third trimester, generally from 37 to 42 weeks, is coined the term of the pregnancy and is sometimes referred by physicians as a fourth separated interval (1).

The significant physiological changes occurring during pregnancy, support and protect the development of the fetus and prepare the mother for parturition. Pregnancy physiological changes differ between early and late periods. During the first periods, hormones, such as human chorionic gonadotropin (hCG), progesterone, estrogens, etc., are the main players of the physiological adaptation

of the mother. In this period, the uterus begins to support the growth of the placenta, amniotic fluid volume augment, and organs start a functional and dimensional change. As an example, maternal heart rate increases from the 5th to the 32nd week, causing an increase of cardiac output of 34–49% and 43–48% by the 12th and 24th weeks of gestation, respectively (2).

During the first week of pregnancy, the hormonal change causes an increase of insulin secretion, and consequently fasting blood glucose may be reduced up to 10–20%. On the contrary, the latter part of pregnancy, especially the third trimester, is characterized by insulin resistance, because of fetus metabolism. Thus, fasting insulin concentration can be doubled with respect to non-pregnant women. In this period, also average plasma glucose can increase.

During pregnancy, there is a rise of kidneys dimension, which drive at least in part, an augmented renal blood flow of 35–60%, which increase the functional capacity of the kidneys. As a consequence, the glomerular filtration rate (GFR) increases of 40–50% by the end of the first trimester, peaking at 180 mL/min. GRF is then maintained at this level until 36 weeks of gestation; after it slightly decreases (3). Therefore, clearance of urea, creatinine and uric acid increase. Nevertheless, increased kidney filtration capability does not cause a marked electrolyte concentration change. Glucosuria may be found in urine due to the increased GFR, which presents more fluid to the tubules and therefore lowers the renal threshold for glucose excretion. Protein loss in the urine can increase to up to 300 mg/day.

Liver dimensions and functions remain almost unchanged. However, laboratory liver tests are often misinterpreted during pregnancy, this mainly because of the significant change in constituent production. Pregnancy hormones alter protein and enzyme synthesis, which markedly changes. An example is alkaline phosphatase, which concentration peaks twofold greater during pregnancy; differently, γ-glutamyl transferase, transaminase and lactate dehydrogenase are less affected by changes. Further, creatine kinase can markedly increase during pregnancy. Lipids, triglycerides and cholesterol have a substantial modification from the second trimester (4).

Several blood coagulation parameters increase, including plasma fibrinogen, factors VII, VIII, IX and X; differently, prothrombin and factor V and XII do not change. As a consequence, prothrombin time (PT) and activated partial thromboplastin time (aPTT) slightly shorten (5,6). Thus, pregnancy can be considered a prothrombotic state. Coagulation factors remain elevated for up to 8–12 weeks post-partum and assays for them may be falsely negative during this period (5). Thyroid-stimulating hormone (TSH) is reduced during the first trimester, returning slowly to normal by the term, while the circulating levels of free T3 and T4 remain fairly constant throughout pregnancy (3).

Furthermore, other numerous hematological, biochemical, metabolic and endocrine constituents are significantly altered during pregnancy and between-trimesters differences are also measurable.

Diagnosis and dating of pregnancy

The diagnosis of pregnancy is based on history and physical examination and laboratory assessment of the hCG. hCG is a hormone produced primarily by syncytiotrophoblastic cells of the placenta during pregnancy and it stimulates the production of progesterone by maintaining the corpus luteum, which, in turn, prevents menstruation. However, several other functions have been described for this hormone (7-9). The conventional pattern of hCG serum concentration during physiological pregnancy shows a rapid increase from 3 weeks after the last menstruation and in the first trimester of pregnancy, doubling about every 40–48 hours during the first 8 weeks, while the peak is usually at about 10 weeks of gestation (weeks since last menstrual period). Eight days after conception, hCG can be detected in the maternal circulation and a concentration of approximately 10 IU/L is observed in serum between the 9th and the 10th day (10). Being the upper reference range (97.5th percentiles) of non-pregnant women ~3.0 IU/L, pregnancy diagnosis can be obtained since nine days after follicular rupture (10). In addition to the intact hCG, other forms of the hormone can be found during pregnancy (11). For example, the beta core fragment (hCGβcf) (12) represents the terminal degradation form of hCGβ and is the principal fragment detectable in urine, whilst it is almost undetectable in serum (11). Therefore, urinary tests present antibodies against hCGβcf. In urine, hCG appearance and rise show similar patterns to those observed in the maternal circulation. The upper limit of the reference range as reported to be ~3.1 IU/L in non-pregnant women with age <50 years and ~4.4 IU/L in those with age >50 years (13). Both serum and urinary tests for hCG are commercially available. However, serum testing is much more sensitive and specific than urine testing because urine assays are claimed to detect hCG levels greater than 20 IU/L. Urinary point of care (POC) devices vary widely in sensitivity for hCG, with sensitivities ranging from

12–50 IU/L (8). Furthermore, several commercially-available urine pregnancy tests do not detect hyperglycosylated hCG, which represent a consistent quantity of hCG in early pregnancy, resulting in a wide range of sensitivities of these tests (9).

Finally, home pregnancy testing can also be used to test pregnancy. However, since their introduction three decades ago, manufacturers have progressively shortened the time of early diagnosis, to the same day of the missed period. A recent study of Cole *et al.* compared different home pregnancy test, using urine collected in well-dated pregnancies. Firstly, the study found that a wide range of hCG levels (from 23 to 2,438 IU/L) can be normally produced by pregnant women by 28 to 30 days after the onset of the last known menstrual period. Considering these ranges, Cole *et al.* calculated that to detect 95% of pregnancies at the time of missed menses, the hCG test would need to consistently detect at least 12.4 IU/L hCG, and, in many circumstances, home tests were not sensitive enough to detect the low hCG levels requested (14).

Common laboratory tests examinations performed during pregnancy

Among the goals of the antenatal care (ANC) programs offered during pregnancy, risk identification and prevention are two important components. To accomplish these purposes, several laboratory tests are usually suggested for all women as part of the usual ANC. Indeed, among the screening/diagnostic procedures suggested during ANC, laboratory tests have been endorsed by numerous governmental or nongovernmental guidelines, including the latest World Health Organization (WHO) (1), the guidelines for perinatal care, American Academy of Pediatrics and the American College of Obstetricians (15), and Gynecologists National Institute for Health and Care Excellence (NICE) (16), Clinical Practice Guidelines from Australian Government (17), and Italian National Guidelines for the physiological pregnancy (18). Despite that, differences are present when guidelines are compared. A summary of laboratory tests routinely recommended to low-risk women are included in *Table 1*.

Some specific considerations should be added. ABO blood group and rhesus D antigens (RhD) type and screened for the presence of erythrocyte antibodies are usually recommended to be tested at the time of the first prenatal visit. Regarding cytomegalovirus (CMV) and Toxoplasmosis, these two tests are not recommended by all the evaluated Guidelines in low-risk women, because the available piece of evidence does not support the routine screening (15-18). Further, internationally, routine testing of pregnant women for hepatitis C virus (HCV) testing is not recommended or recommended only in high-risk women (15-18), with the except of the Australian guideline (17). The utilization of CMV testing as ANC screening is discussed in all the fourth guidelines, albeit it is not recommended. Gonorrhea evaluation is suggested in case of risk factors (18).

Rh blood type and antibody screening for red blood cells (RBC) alloimmunization

The genes *RhD* and *RhCE* encode the RhD and RhCE for erythrocyte membrane proteins that are antigenic. Both genes are 97% identical and are located in tandem on chromosome 1p34–p36 at about 30 kb apart. Each gene contains ten exons, span a 75 kb DNA, sequence and are the result of genes duplication (6,19,20). In CD nomenclature, RhD and RhCE are termed CD240D and CD240CE (20). Unlike the other blood groups antigen, Rh proteins are expressed only in the membranes of RBC and their intermediate precursors.

The presence or absence of Rh proteins on the RBC membrane (C, D and E antigens) determine the Rh phenotype. However, being RhD protein the most important antigen, this phenotype is mostly considered for alloimmunization. Individuals with RhD negative are approximately 15% of Caucasians, 5% of Africans, and less than 1% of Asians (21). Moreover, variants of D antigen have been described and well documented since now, such as D^U or "weak D". D^U is a Rh phenotype found in less than 0.2–1.0% of Caucasians (22) and it was demonstrated that women with a D^U phenotype, when exposed to RhD positive RBC by transfusion or pregnancy, formed anti-D antibody (23). Finally, other Rh antigens can provoke the antibodies formation and should be inspected (24).

Determination of Rh blood groups is of utmost importance for pregnant women. During pregnancy, Rh-negative women can develop antibodies against Rh antigens in response to maternal exposure to Rh-positive fetal RBC. Studies have estimated that approximately 15% of unprotected women who are Rh-negative will develop alloimmunization (25). Sensitized mother can develop antibodies against Rh-positive cells, a severe condition known as Rh incompatibility or hemolytic disease of the newborn (HDN). The women at greatest risk for

Table 1 Routine laboratory test recommended to low-risk women by different guidelines for monitoring physiological pregnancy

Suggested period*	Condition	Laboratory tests	Guidelines recommending the test(s)
I trimester	HDN	Blood group and rhesus factor and check for antibodies against RBC	A; B; C; D
I trimester and III trimesters	Anemia, hemoglobin disorders	Complete blood count	A; B; C; D
I trimester	Asymptomatic urinary tract infection	Urine culture and urinalysis	A; B; C; D
I trimester	Infections that cause newborn defects	Rubella, toxoplasmosis	C (rubella); D
I trimester	Prevent transmission of syphilis to newborns	VDRL/RPR (nontreponemal tests)	A; B; C; D
I trimester	Severe viral infections, potentially transmitted to the newborn	HIV, HBV, HCV	A (only HIV and HBV); B (only HIV and HBV); C; D (only HIV and HBV)
I trimester	Hyperglycemia	Plasma glucose	Depending on risk factors and the availability of pre-conception values
I trimester	Chlamydial infection	Chlamydia	A; C (for women <30 years of age); D (for high-risk women)
II trimester or III trimesters (24–28 weeks)	Gestational diabetes	(fasting and/or following oral glucose loading)	A; B (in high-risk women); C; D
III trimester	Prevent group B streptococcus infection in newborns	Group B streptococcus	A; C; D

*, Suggested periods are not reported by all the guidelines and may vary between guidelines; A, Guidelines for Perinatal Care, American Academy of Pediatrics and the American College of Obstetricians and Gynecologists, 7th edition, USA; B, National Institute for Health and Care Excellence, NICE, UK; C, Clinical Practice Guidelines, Pregnancy Care, Australian Government, Department of Health, Consensus based recommendations; D, Physiological Pregnancy Guideline, Italian Department of Health. HDN, hemolytic disease of the newborn; RBC, red blood cells; VDRL, venereal disease research laboratory; RPR, rapid plasma reagin; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus.

delivering infants with HDN are Rh-negative mothers with Rh alloantibodies who conceive Rh-positive babies and are in the second or subsequent pregnancies (26). HDN can affect both the fetus and the newborn and is caused by the presence in fetus circulation of maternal antibodies against the erythrocyte membrane Rh-proteins. Antibodies in maternal blood are actively transported through the placenta and once reached the fetus, and they can react against the fetal erythrocyte, which is eventually destructed in the fetal spleen causing fetal anemia. Mild or moderate hemolysis in the fetus causes an increase in the indirect bilirubin, which appear in the amniotic fluid. Severe hemolysis can cause anemia with extra work for the fetal hearth for providing sufficient oxygen to the tissues with subsequent damage of the liver (24). This situation represents a severe condition, known as erythroblastosis fetalis, and is life-threatening both for the fetus and the newborn. Doppler ultrasonography of the middle cerebral artery is recommended to identify fetuses at risk for moderate to severe hemolytic disease (24). In addition to the Rh-negative hemolytic disease also ABO negative hemolytic disease and hemolytic disease due to alloantibodies other than Rh groups (e.g., anti-Kell) comprise the complete spectrum of HDN.

The ABO/Rh typing, as well as the antibody screening for RBC alloimmunization (indirect antiglobulin method, Coombs test), are routinely performed at the first prenatal visit (preferably first trimester) on the mother blood (*Table 1*). Antibody screen includes a search against a standard panel of RBC and is used to determine if there are maternal alloantibodies (such as those against RhD, Rhc, RhE and anti-Kell). In the case of the positive indirect antiglobulin test, the diagnosis of alloimmunization of the women can be made (27) and the condition should be managed to avoid the

development of HDN. In general, women with titers higher than 1:4 should be considered Rh alloimmunized (24,28), although studies of critical titer are quite disparate (6). Titers tend to correlate more reliably with the severity of fetal disease in the first sensitized pregnancy than in subsequent pregnancies (28). The management of the women with alloimmunization is of very important in order to the initial assessment of the risk of HDN. In particular, the genetics of Rh of the father should be inspected to evaluate the homozygosity for the antigen corresponding to the maternal antibody. The parental zygosity is used to define the risk of incompatibility (100% for homozygous and 50% for heterozygous father, respectively). If the father does not bear the allele, it will confirm the fetal negativity for that antigen, in which case there would be an absence of risk of HDN. Differently, if the father is heterozygous, fetal genotyping from cultured amniocytes could be used to determine the genetics of the fetus, especially in the case of high titer of mother's alloantibody (>1:32) (24). The likely future direction of prevention of HDN lies in defining the fetal genotype from cell-free fetal DNA (cffDNA) in maternal plasma. In fact, a slight but detectable amount of cffDNA is released from the placenta of pregnant women into the maternal circulation, where it mixed together with the much larger women's own cfDNA (29). In a recent meta-analysis, the evaluation of cffDNA showed a summary sensitivity of 0.993 [95% confidence interval (CI), 0.982–0.997] and a specificity of 0.984 (95% CI, 0.964–0.993) for the evaluation of fetal RhD genetics (30). For sensitized mothers with an at-risk fetus, serial titers are performed on maternal serum every month until 24 weeks' gestation, and then every 2 weeks thereafter (6,24).

Complete blood cell (CBC) count

Pregnant women present different CBC ranges. During gestation, blood volume increases of approximately 1,500 to 1,600 mL (40–50%). Plasma volume increases in percent more than the RBC mass. Thus, hemoglobin (Hb) concentration and RBC count (and hematocrit) physiologically decrease during pregnancy, despite the increased erythropoiesis. For example, Hb concentration at term average 126 g/L, compared with 133 g/L of non-pregnant women. This aspect is called physiological anemia of pregnancy and it represents a physiological status, while both low and high Hb concentrations are associated with worse outcome (31). It should be considered that Hb reference intervals vary during pregnancy (before pregnancy 117–153 g/L, while during pregnancy 113–147 g/L at 13–20 weeks, 111–143 g/L at 21–28 weeks, 109–145 g/L at 29–34 weeks, 110–147 g/L at 35–42 weeks and 108–156 g/L at delivery) (32).

CBC should be routinely offered to pregnant women for identifying pathological conditions (e.g., anemia), to support the diagnosis of infection or to suggest further inspection for hemoglobinopathies. Condition of pathological anemia has been claimed to be the most common disorder in pregnancy, with a worldwide prevalence of 41.8% (33). The WHO criteria for mean minimum normal Hb concentration in healthy pregnant women is 110 g/L in the first half of pregnancy and 105 g/L in the second (17,34). Hb concentration is usually measured during the CBC routinely, offered during pregnancy (*Table 1*). In a recent meta-analysis, low Hb concentration at below 90 g/L, 100 and 110 g/L had respectively a 72% [odds ratio (OR), 1.72; 95% CI, 1.30–2.26], 33% (OR, 1.33; 95% CI, 1.17–1.52), and 10% (OR, 1.10; 95% CI, 1.02–1.29) risk of preterm birth (33). Hb concentration below 90, 100, and 110 g/L had, respectively, 2.14 (95% CI, 1.57–2.91), 1.57 (95% CI, 1.30–1.90), and 1.17 (95% CI, 1.03–1.32) times significantly higher risk of low birth weight delivery when compared with pregnant women with Hb concentration 110–139 g/dL (33). Moreover, Hb concentration below 100 or 110 g/L increase the risk of small-for-gestational-age of 26%, (95% CI, 9% to 45%) and 14% (95% CI, 5% to 24%) (33). An increased risk for small-for-gestational-age was also found for elevated levels of Hb (>146 g/L) (35). Iron deficiency, but also deficiency of folate, vitamin B12 or hemoglobinopathies can cause anemia. Iron deficiency anemia is the most frequent hematological concern during pregnancy, with a prevalence low (<20%) or high (>35–75%) in developed and developing countries, respectively (17). Iron deficiency anemia is usually characterized by decreased levels of Hb, mean cell volume (MCV) and mean cell hemoglobin (MCH). When iron deficiency anemia is suspected, a measurement of serum ferritin should be used to confirm the diagnosis. Serum ferritin reference intervals vary deeply during pregnancy (before pregnancy 5.0–60.5 μg/L, while during pregnancy 7.1–106.4 μg/L at 7–17 weeks, 4.1–65.6 μg/L at 17–24 weeks, 3.8–49.8 μg/L at 24–28 weeks, 4.2–39.0 μg/L at 28–31 weeks, 4.3–40.5 μg/L at 31–34 weeks and 4.8–43.5 μg/L at 34–38 weeks) (36). Iron dietary supplementation is not generally suggested to all women during pregnancy, especially considering the potential risks of indiscriminate iron supplementation (31).

CBC is also useful for RBC, WBC and platelets counts.

RBC and hematocrit decline at the first trimester, reaching their lowest point at second trimester and begin to increase at the third trimester. The RBC indices, namely MCV, MCH and mean corpuscular hemoglobin concentration (MCHC), varied during pregnancy, especially in the first trimester (37). White blood cell (WBC) count increase during pregnancy and a slight leukocytosis is considered normal as induced from the physiological stress of the pregnant status. Platelets usually decrease, during the third trimester. This is called "gestational thrombocytopenia" and it is partly due to hemodilution and/or increased platelet activation and accelerated clearance (5).

Glucose testing

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. Approximately 7% of all pregnancies are complicated by GDM, resulting in more than 200,000 cases annually (38). Recently, the American Diabetes Association redefined it as "diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes" (39). GDM is often asymptomatic but increases the risk of macrosomia, shoulder dystocia, birth injuries, hyperbilirubinemia, hypoglycemia, respiratory distress syndrome, and childhood obesity. Furthermore, the risk of adverse perinatal outcomes is associated with the degree of hyperglycemia (38).

ANC guidelines have a different recommendation for GDM (38). Screening is suggested on the basis of risk factors for GDM. Clinical characteristics consistent with a high risk of GDM are marked obesity, personal history of GDM, glycosuria, or a strong family history of diabetes. Women with these characteristics are advised for glucose testing as soon as feasible. On the contrary, some guidelines state that no glucose testing for GDM is required in low-risk women (40). In the guidelines for perinatal care from the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists, screening for gestational diabetes should be offered at 24–28 weeks and can be done in the fasting state or fed state. A 50-g oral glucose challenge test is given followed in 1 hour by a plasma test for the glucose level. Different screening thresholds (ranging from 7.2 to 7.8 mmol/L) are utilized, and those are meeting or exceeding this threshold undergo a 100-g, 3-hour diagnostic oral glucose tolerance test (15). NICE, The Clinical Practice Guidelines, Pregnancy Care, Australian Government, Department of Health and the Italian National Guideline recommend a 75 g, 2 hours OGTT only for women at risk of diabetes, which is the WHO suggested criteria for diagnosing diabetes both during and outside pregnancy (16-18). However, it could be important to discriminate between GDM and overt diabetes, a condition of pre-existing diabetes to be determined at the first antenatal visit. Italian National Guideline recommends fasting plasma glucose (FPG) measured at the first appointment in case that any recent previous diabetic conditions are not available (18). Similarly, when a woman has risk factors for hyperglycemia in the first trimester, Australian Guidelines suggest as suitable tests fasting blood glucose or glycated hemoglobin (HbA1c) (17). Currently, the latest evidence supports that metabolic syndrome, when assessed early in pregnancy, is a strong risk factor for GDM and predict its occurrence (41).

Screening for aneuploidy

The purpose of the screening test during pregnancy is to assess the woman's risk of carrying a fetus with aneuploidy, defined as the genetic condition of carrying one or more extra or missing chromosomes (42). Guidelines generally recommend offering the option of aneuploidy screening tests to all pregnant women (43). The purpose of prenatal screening for aneuploidy is to provide an assessment of the woman's risk of carrying a fetus with one of the more common fetal aneuploidies, namely trisomy 21 and 18 (and in some instances trisomy 13). There are several types of screening tests, which can be performed in all trimesters of pregnancy (42). However, the type of screening depends on risk factors, including (but not limited to) age, family history, fetal findings, exposures, and patient preferences (43). Serum screening tests (or biochemical screening tests) are the most frequently used type of screening tests in pregnancy (43). First-trimester screening tests are typically executed during the 10^{th} and the 13^{th} weeks of gestation and include: (I) a nuchal translucency measurement, (II) pregnancy-associated plasma protein A and (III) serum free β-hCG (or total hCG) levels. Detection rates range from 82% to 87% for trisomy 21 (43). Second-trimester screening (also known as quadruple screen or quad screen) can be performed approximately between the 15^{th} and the 22^{nd} week of gestation and this test does not require the ultrasonography for nuchal translucency. The quad screen involves the measurement of (I) hCG, (II) alpha-fetoprotein (AFP), (III) dimeric inhibin A, and (IV) unconjugated estriol, in combination with maternal factors such as age, weight, race, the presence of diabetes. In the last decade, cffDNA has been widely integrated into routinely

prenatal screening test for aneuploidy. Initially, the scope of cffDNA test was the detection of trisomy 21, 18 and 13. However, the purpose of this test has been soon expanded to include sex chromosome aneuploidy and microdeletion panel (44). Screening for Down syndrome can be performed by cffDNA from 10 weeks of gestation and offers the highest reported detection rate, with more than 98% detection with positive screening rates of less than 0.5% among women with a reportable result. However, the rate of detection is lower for trisomy 18 and 13 (42).

Conclusions

Laboratory medicine plays a major role in monitoring physiological pregnancy. The monitoring of pregnancy is considered as part of the routine examination for pregnant women and it is included in National and International ANC Programs. Monitoring of pregnancy physiology offers the opportunity of preventing and detecting morbidities and other pathological conditions during this period. Moreover, technological advancements are rocketing and, currently, several new biological markers are under evaluation or implementation for evaluating women's and fetus' health or the presence of pathological conditions. In this scenario, laboratory medicine tests represent part of the ANC support offered to women during the whole pregnancy period, starting from the determination of the status until the delivery. This fact is recognized, albeit with some variant, by all ANC international guidelines.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Giuseppe Lippi, Martina Montagnana and Zhi-De Hu) for the series "Laboratory Medicine in Pregnancy" published in *Journal of Laboratory and Precision Medicine*. The article has undergone external peer review.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jlpm.2019.12.02). The series "Laboratory Medicine in Pregnancy" was commissioned by the editorial office without any funding or sponsorship. The author has no other conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/jlpm.2019.12.02
Cite this article as: Padoan A. Laboratory tests to monitoring physiological pregnancy. J Lab Precis Med 2020;5:7.

