PEDIATRIC AND MATERNAL-FETAL DIVISION NEWS
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AACC Better health through laboratory medicine.

TABLE OF CONTENTS

FROM THE MIND OF THE CHAIR

It is my pleasure to serve as division Chair for the next 2 years. This is an exciting time for our areas of expertise in pediatric and maternal fetal laboratory medicine and will bring many opportunities for engagement with you, our members. I would like to thank Dr. David Carpentieri for his leadership of the division, which was recognized in 2015 by AACC President, Dr. David Koch, for contributions to AACC's advocacy efforts. We will continue our efforts in advocacy, education and community and hope you will join us.

You will note that our division newsletter has been revised and condensed to bring you similar content in fewer pages. In this issue, we continue our ABC's of Laboratory Medicine with letter 'W', focused on 'Wrong Test Ordered.' Our 'Interview with a Colleague' segment features Dr. David Koch, AACC's 2015 President. In case you missed it, the newsletter editorial team provides a brief wrap-up of PMF-related events and awards from the 2015 Annual Meeting. Also in this edition: the election results are in! Find out who will serve as division officers. Finally, our division page on AACC's Artery is live and active - come connect with us in the PMF community forums to seek advice and find out what your colleagues are discussing.

I hope that you enjoy this edition of the newsletter and that you will join us in our future efforts to advance the practice of pediatric and maternal fetal laboratory medicine. All the best in 2016!

Shannon Haymond, PhD
Chair, AACC PMF Division

THE ABC'S OF PEDIATRIC LABORATORY MEDICINE:

W IS FOR "WRONG TEST ORDERED!"

Laboratory testing is the highest volume medical activity (1). Overutilization and misutilization of laboratory tests can lead to diagnostic error, unnecessary blood draws and medical interventions, increased costs and adverse outcomes. In this series of *ABC's of Pediatric Laboratory Medicine*, we highlight wrong tests used in pregnant and pediatric populations. The following four vignettes illustrate obsolete or misused tests in screening for pregnancy status, thyroid function during pregnancy, HIV screening in neonates and vitamin D deficiency.

Qualitative hCG- An Obsolete Test

Kushbu Patel, PhD
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Point-of-care human chorionic gonadotropin (hCG) testing is often used in emergency departments and outpatient clinics to rule out pregnancy before performing interventions that may harm a developing fetus. Some qualitative point-of-care devices, referred to as hCG combo tests, are FDA approved for use with either urine or serum. For such devices, urine is preferred over serum as it requires no sample processing and can be performed at the point-of-care. Qualitative serum hCG tests are often ordered because of their perceived faster turnaround time (2, 3). Since qualitative serum tests cannot be performed at the point-of-care due to the need for centrifugation, their turnaround time is usually comparable to quantitative hCG assays using plasma specimens. Additionally, the analytical sensitivity of qualitative tests is inferior to quantitative tests (10 IU/L vs. 1 IU/L). Given that the clinical use of qualitative serum hCG test is to detect a possible pregnancy, the most sensitive test should be used.

As with most immunoassays, there are limitations to both qualitative and quantitative hCG assays, as both types of assays are prone to false negatives due to the high-dose hook effect (4) and false positives due to heterophile antibody interference (5). Because antibodies are filtered in the glomeruli, heterophile antibody interference is seldom present in urine samples. Interestingly, there have been case reports demonstrating heterophile antibody interference in qualitative but not quantitative serum hCG assays (5, 6). To summarize, serum is a technically demanding specimen and qualitative hCG devices, and their analytical performance, is inferior to quantitative hCG tests that are readily available in most clinical laboratories. For these reasons, the qualitative serum hCG testing is considered obsolete.

Assessment of Thyroid Function During Pregnancy

Alison Woodworth, PhD
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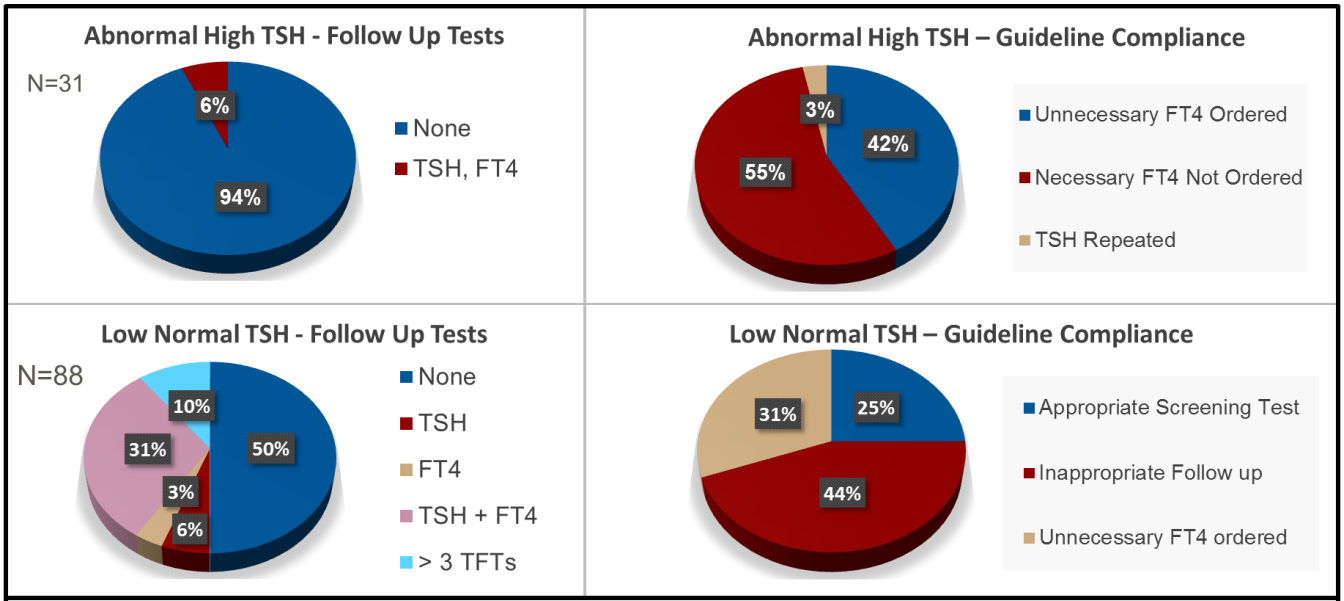
Maternal thyroid dysfunction during pregnancy can lead to significant morbidity and mortality for both mother and fetus. Laboratory testing is essential to establishing a diagnosis of thyroid dysfunction, particularly in subclinical disease, as clinical signs and symptoms are non-specific in pregnancy. International Thyroid, Endocrine, and Obstetrics and Gynecological societies' guidelines recommend testing for thyroid dysfunction in pregnancy by measuring Thyroid Stimulating Hormone (TSH). Any abnormal TSH result, considered in the context of trimester specific reference intervals established at each testing site, should be followed with Free Thyroxine (FT4) testing (7-10). Although there are proven benefits of treatment of thyroid dysfunction during pregnancy, lack of evidence has precluded most professional societies from recommending universal screening of asymptomatic pregnant women for thyroid



Thyroid Function Screening and Follow Up Testing at Vanderbilt OB Clinics. Follow up testing and practice guideline compliance were reviewed in patients where TSH results where abnormal for either the non-pregnant (NPRI) or the trimester specific reference intervals (TSRI). **Abnormal high TSH** values are normal by NPRI, and high by TSRI. **Low Normal TSH** values are Low by NPRI and normal by TSRI.

dysfunction. Despite recommendations for targeted screening of high risk patients, in practice the majority of clinicians have endorsed and/or implemented universal screening for thyroid dysfunction in pregnancy (9). At Vanderbilt, we conducted a study to review current ordering practices and facilitate compliance with evidence based recommendations for thyroid function testing in normal pregnancies.

Laboratory Information System (LIS) records from a 6 month time period (12/1/2014 – 5/30/2015) were reviewed. All patients with an RPR ordered (syphilis testing - a mainstay among pre-natal labs) under ICD9 Codes V22 (Normal Pregnancy) and/or V72.42 (Pregnancy test positive) by a Vanderbilt Obstetrics or Midwifery practice during the enrollment period were included. Patients <18 years, pregnant with multiples, and/or a history of thyroid disease were excluded. Thyroid function testing results for the study participants +/- 9 months from the initial RPR tests were collected from the LIS database. Patients' Electronic Medical Records were reviewed to determine follow up to thyroid function testing results.

Our study revealed that adherence with practice guidelines' recommendations for thyroid function testing in pregnancy was intermittent in healthy patients. Among 1672 included pregnancies, 1077 were screened for thyroid dysfunction. Among those screened, 496 had TSH testing only, while 583 had combined TSH and FT4 testing. Clinical follow up for those screened appeared to be based on non-pregnant reference intervals (Figure 1).

Root cause analysis revealed two problems: (1) TSH and FT4 were bundled in an electronic order set for first time prenatal labs in some of the OB clinics and (2) Trimester specific reference intervals were not visible in the EMR. Therefore we worked with our clinicians to remove FT4 from the new OB electronic order sets and with our EMR team to add appropriate reference intervals, both of which will help to reduce inappropriate ordering and misinterpretation of thyroid function tests in pregnancy. We also found that screening for thyroid dysfunction in pregnancy was indiscriminate and differed by practice, which may reflect the current state of the field. More consistent practice of thyroid testing in pregnancy requires large clinical trials looking at

diagnosis and management of thyroid dysfunction in normal pregnancies.

HIV Screening in Neonates

Kushbu Patel, PhD

HIV screening in exposed infants allows for early diagnosis, ensuring timely initiation of treatment and prevention of opportunistic infections. The fourth generation combination HIV antibody/ antigen tests used in adults are not suitable for screening infants. Maternal HIV antibodies can cross the placental barrier and persist up to 18 months, leading to false positive serology testing (11). Therefore, nucleic acid tests are ideal for the earliest detection of a likely HIV infection in newborns.

Current guidelines recommend diagnostic testing in HIV exposed infants be performed at 14-21 days, 1-2 months, and 4-6 months (12). HIV DNA PCR can detect viral DNA with a sensitivity of >65% at birth, which improves to >90% at 2 weeks of age and is 100% at 3 months (13). Until recently, AMPLICOR® was the most widely used HIV-1 DNA test in infants; however, it is no longer commercially available in the United States. Non-commercial HIV-1 DNA tests are offered by other laboratories; however, their sensitivities and specificities may vary.

RNA amplifying tests are more readily available because of their use in monitoring viral loads in HIV-positive patients. Quantitative, RT-PCR based RNA assays detect extracellular viral RNA in the plasma. The sensitivity of HIV-1 RNA assays is ~25-58% in infants less than <1 week of age, improving to 100% at 3 months (14). In general, DNA and quantitative RNA assays are considered equally sensitive and specific. However, RNA assays can potentially be affected by antiretroviral treatment (ART) (14, 15) and HIV RNA levels <5000 copies/mL are not reproducible requiring a second confirmatory test. Most guidelines recommend DNA testing as a first line screening tool in infants, with confirmatory testing with quantitative RNA assays.

Vitamin D Testing

Anna Merrill, PhD
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Vitamin D is a fat-soluble compound that plays an important role in calcium and phosphorus homeostasis and bone metabolism. Deficiency of this micronutrient can lead to rickets and osteomalacia in the pediatric and adult populations, respectively. Current Endocrine Society and US Preventive Services Task Force (USPSTF) guidelines recommend screening individuals *at risk* for vitamin D deficiency. High risk groups include non-supplemented, breast-fed infants and pregnant and lactating women. Growing clinical attention to vitamin D has prompted a substantial increase in the demand for vitamin D-related laboratory testing and, along with it, the propagation of mistaken notions regarding such testing (16). Vitamin D is activated by various hydroxylation events, with 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D produced by hepatic and renal metabolism, respectively. Though 1,25-dihydroxyvitamin D is the most active form of vitamin D, it is not a good marker of overall vitamin D nutritional status and is often ordered in error (17). When assessing vitamin D stores, 25-hydroxyvitamin D is the better test for three main reasons: longer circulating half-life (2–3 weeks) and significantly less day-to-day biological variability compared to the short-lived 1,25-dihydroxyvitamin D (half-life of 4-6 hours); 1000-fold higher serum concentrations of 25-hydroxyvitamin D compared to 1,25-dihydroxyvitamin D (a considerable analytical advantage); and the relationship between 1,25-dihydroxyvitamin D concentrations and vitamin D stores is obscure since the former is regulated primarily by parathyroid hormone, meaning that 1,25-dihydroxyvitamin D concentrations may actually rise in situations of vitamin D deficiency.

Measurement of serum 1,25-dihydroxyvitamin D does have clinical value for select patient populations (e.g., patients with acquired or inherited vitamin D disorders, including renal failure, granulomatous disease, or suspected rare errors of vitamin D metabolism). However, 25-hydroxyvitamin D is the most useful in nutritional assessment and, therefore, most commonly the correct test to order.

Signorelli et al. (18) investigated ordering patterns of vitamin D-related tests in a benchmarking study that compared 81 similar institutions. Ordering of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D varied considerably, with many institutions exhibiting possible overutilization of 1,25-dihydroxyvitamin D. Many facilities have successfully implemented intervention techniques to improve utilization of 1,25-dihydroxyvitamin D.

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INTERVIEW WITH A DISTINGUISHED COLLEAGUE

DAVID KOCH, PHD
2015 AACC PRESIDENT
PROFESSOR, EMORY UNIVERSITY, ATLANTA, GA

How has AACC helped promote or support pediatric and/or maternal-fetal laboratory medicine?

AACC has ramped up our advocacy efforts in the past year or so; notable for pediatrics and maternal-fetal lab medicine is work done to promote newborn screening and secure legislative support for that aspect. AACC also held its first ever Congressional Briefing in Oct. of 2014; the topic focused on children's health. Several visits to Capitol Hill have occurred this past year, on matters such as newborn screening and lab-developed tests.

AACC continues to provide valuable continuing education to its members through webinars, meetings, and publications. I will specifically highlight the relatively new Mass Spec Division which held a meeting in Chicago this fall. One of the areas discussed was the application of mass spec to newborn screening. In addition, Clinical Chemistry's January edition is a special issue on clinical mass spectrometry.

AACC is also proactively reaching out to the news media more than ever before, helping to build AACC's reputation as a credible, valued resource for reporters and media show hosts.

What changes do you see in the future of pediatric and/or maternal-fetal laboratory medicine?

The changes I see coming in these areas of laboratory medicine are similar to changes that will affect our entire field, wherever we work. Technology and analytical innovation will continue to be available, and we must work to deploy those tools that will best improve laboratory medicine's impact on health care. Special mention here to mass spectrometry, the use of which I'm sure will continue to expand in pediatrics and newborn screening.

Wrap Up: Highlights from the 2015 Annual Meeting and Clinical Lab Expo

Glucose analysis in the pediatric and neonatal intensive care unit

Brad Karon, MD, PhD

Assistant Professor, College of Medicine, Mayo Clinic, Rochester MN

At the Pediatric Maternal Fetal division Hot Topics session during the 2015 AACC annual meeting, one topic of discussion was glucose testing, specifically glucose testing done at the bedside with hand-held glucose meters. While this practice has been nearly universal in hospitals for adults, children, and infants, recent actions and interpretations by the Food and Drug Administration (FDA) and Center for Medicare Services (CMS) have called current practice into question. After public forums and discussion dating back to 2010, and in response to multiple FDA statements regarding the limitations and intended use of glucose meters in the hospital, CMS issued a draft memo to state surveyors in November 2014 regarding glucose meter use in the hospital. The memo pointed out that like all waived laboratory tests, use of glucose meters must conform to the manufacturer's intended use and limitations in order to maintain the waived status of the device. For glucose meters, this is significant because no device has been approved for use in all critical care populations with all sample types, and some devices currently in use do not carry any indications at all for use in critically ill patients. For infants and children, this means that using a glucose meter within the pediatric or neonatal intensive care unit may be considered an "off label" use of the device. Under these circumstances, method validation, quality control, personnel requirements (and more) would have to meet those of a high complexity, rather than waived device. For many institutions (depending upon device used, sample types used, operator training, etc), the end implication of this new oversight is that nurses may no longer be able to perform glucose meter testing on critically ill infants and children. Further confounding the issue, some glucose meters list hyperosmolar hyperglycemia as a device limitation, thus creating confusion about whether one of the more common uses for glucose meters in the pediatric ICU (monitoring of diabetic ketoacidosis) is "off label" or waived, and what if any specific validation is necessary to use meters to monitor children with diabetic ketoacidosis. In response to the confusion created by the release of the November 2014 memo, CMS withdrew the memo in March 2015 to gather more information about its potential impact. However, in the meantime both CMS and accrediting agencies have said they will continue to enforce the concept that waived devices must be used according to their indications and limitations, or be validated and used as high complexity tests. We are sure to hear much more about this issue in the months to come.

SYCL-PMF Division Raffle Winner

This year the PMF Division raffled off an annual Division membership to a member of the Society for Young Clinical Chemists (SYCL) during the SYCL Mixer. Kelly Doyle, PhD from Intermountain Health in Salt Lake City, Utah was the lucky winner. Welcome to the Division, Kelly!

Up and Coming!

PMF is LIVE on the AACC Artery

The PMF division is now live on the AACC Artery. Moving into 2016, our division website and listserv are now fully transferred to the AACC Artery. The AACC Artery is a private online community of laboratory medicine

professionals accessible only to AACC members. You can visit our division website on the Artery by logging into AACC and finding the Artery under the Community tab. Once logged into the Artery, our Artery page is listed under the Divisions drop down tab. On the PMF Artery page, you can:

1. Post questions on issues related to pediatric and maternal/fetal laboratory medicine and get feedback from members with expertise in these areas of laboratory medicine.
2. Read about the latest news related to our division.
3. Easily communicate with other division members.
4. Search the resource center for our past newsletters and other documents related to our division.

Our current Artery moderators are John Mills and Sharon Geaghan. We'll be trying to engage our membership on the Artery to maximize the functionality of the Artery for our members. We'd love to hear your questions and suggestions on the PMF forum.

PMF Election Results

Officer elections were held at the end of 2015. Congratulations to the following individuals:

Chair-Elect (2016-2017)

Alison Woodworth, PhD; Vanderbilt University

Member at Large (2016-2018)

John Mills, PhD; Mayo Clinic

Member at Large (2016-2018)

Joely Straseski, PhD; University of Utah/ARUP Laboratories

Thank You for your Service!

The PMF Division wishes to thank individuals that have completed their position term or are moving on to new positions. We sincerely thank David Carpentieri, PhD (Chair) Sharon Geaghan, MD (Past-Chair), Jon Nakamoto, MD, PhD (Member at Large), Alison Woodworth, PhD (Member at Large), John Mills (Fellow) and Joely Straseski, PhD (Newsletter Editor) for their services and commitment to our Division. Together we work toward the common goal of improving pediatric and maternal-fetal medicine.

2016 PMF Division Executive Board:

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Chair Elect
Alison Woodworth, PhD

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