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

FROM THE MIND OF THE CHAIR

Hi PMF Division Members!

Happy New Year! Thanks for checking out the Winter 2019 edition of our newsletter! I am so excited about all that our Division accomplished in 2018! We worked to engage our members by planning several networking and scientific sessions at the Annual Scientific Meeting in Chicago and increasing the content on the artery – check out our cases and quiz questions if you haven't already! We supported the Government and Advocacy Committee to provide content distributed as part of the pediatric reference interval advocacy work on Capitol Hill and we participated with AACC to further work with their pediatric reference interval research initiative. We also published a Q&A report in Clinical Chemistry on Polycystic Ovarian syndrome – coming soon.

I want to send a special thanks to Drs. Joely Straseski and John Mills for their service on the board for many years as their terms have ended! With recent nominations and elections, we were ecstatic that so many of our members are interested in serving on the PMF board! For those of you interested in serving, but not chosen this time, we have many exciting new initiatives coming this year and encourage you to get involved! Please contact me if you are interested in participating in any of our upcoming initiatives or have ideas for new projects:

- Pediatric Reference Interval Project in collaboration with AACC and NHANES
- Pediatric Laboratory Medicine Curriculum development
- Guidance documents on Pediatric and Maternal/Fetal laboratory test utilization in collaboration with the Science and Practice Core Committee

In this issue, we continue our ABC's of Pediatric Laboratory Medicine series with our "C" installment on Copper. In the Interview with a distinguished colleague piece, AACC president elect, David Grenache shares with me his vision for his presidency and the future of Pediatric and Maternal/Fetal Laboratory Medicine. Then in our excerpts from the literature segment, Kelly Doyle discusses the recently signed Preventing Maternal Deaths Act of 2018 and its impact on the clinical laboratory.

Finally, the election results are back and we have two new members at large on our board! Check out our new PMF executive board listed at the end of the newsletter!

I hope you find the content of this newsletter both interesting and helpful! Thank you for your ongoing support of the efforts of the PMF Division! Please reach out to me if you are interested in serving on a PMF committee or have ideas for future newsletter content!

Alison Woodworth
Chair, AACC PMF Division

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THE ABC'S OF PEDIATRIC LABORATORY MEDICINE:

"C" is for Copper Imbalance and its Associated Disorders

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Significance and Physiology of Copper:

Copper is an essential trace element and cofactor for cuproenzymes that mediate multiple physiological reactions in the body including hematopoiesis, iron-hemoglobin binding, bone mineralization, immune functions, and melanin formation [1, 2]. Maintaining a steady supply and balance of copper levels is vital for supporting proper cuproenzyme function. For instance, the function of cross-linking cuproenzyme lysyl oxidase, which is involved in the formation of collagen and elastin, can be disturbed due to copper deficiency, potentially affecting the integrity of the connective tissue [3].

Dietary copper is ingested partially absorbed in the acidic environment of the stomach but primarily through intestinal lumen of the duodenum and ileum [4]. Copper uptake in enterocytes is facilitated via membrane transport protein, CTR1. Copper is then shuttled by chaperone proteins including Cox17, Cu-transporting ATPases, ATP7A or ATP7B, which facilitate copper distribution to mitochondria, the Golgi network, and other organelles [4, 5]. Copper enters blood circulation via plasma transport proteins including albumin and ceruloplasmin [6]. Ceruloplasmin not only functions as the major circulating transport protein for copper but is also a cuproenzyme which plays a critical role in iron oxidation. It is shown that plasma levels of ceruloplasmin significantly decrease following dietary copper deficiency in rodents [7].

In the United States and Canada the Recommended Dietary Allowance (RDA) is 900 µg/day for adults, 200 µg/day for infants, and 260 µg/day for children between 1-3 years [8]. There is an increased need of copper intake during pregnancy and lactation [8]. Interestingly, copper absorption and bioavailability can be modified by several factors such as age, sex, copper source, acidic pH and dietary macronutrients [6].

Mechanisms and Clinical Manifestations of Copper Deficiency/Overload:

In developed countries, including the United States, copper deficiency is a rare condition. However, states of copper insufficiency can occur due to acquired or inherited conditions [4]. The most common known acquired conditions in adults are malabsorption following an inflammatory bowel disease, celiac disease, or prolonged diarrhea; post-surgery (bariatric) malabsorption; zinc-induced copper deficiency; and dietary antagonists [9-12]. Several case studies have also demonstrated the development of copper deficiency following gastrectomy [13], gastric bypass surgery [14-16], zinc supplementation [17] and parenteral nutrition [18-20].

Copper deficiency is also reported in cases of premature newborns and low birth-weight infants, who require sufficient copper nutrition for their appropriate skeletal and brain development [21, 22]. The majority of prenatal liver copper accumulation occurs during the last trimester of gestation, leaving premature infants with significantly reduced circulating concentrations of copper and ceruloplasmin [23]. In these cases, awareness and early diagnosis of copper deficient conditions is of great significance, as treatment with adequate copper supplementation in malnourished infants can improve energy intake and weight gain as well [24].

Copper deficiency is classically characterized by hematological manifestations, including neutropenia in early stages, followed by hypochromic anemia, abnormalities in iron, glucose and cholesterol metabolism, and fracture of long bones [25]. Hypopigmentation also occurs due to the impaired catalytic activity of cuproenzyme tyrosinase [25]. Individuals with prolonged copper deficiency can also develop irreversible neurologic symptoms such as central nervous system demyelination and optic neuritis [26]. The association of acquired copper deficiency with myelopathy was first reported in 2001 [27], with additional neurologic signs and symptoms of acquired copper deficiency confirmed later in multiple case reports [14, 28-35]. These patients present with sensory ataxia, gait difficulties, paraesthesia and spastic paraparesis [30]. Some neurologic symptoms are similar to those observed in vitamin B12 deficiency [2, 33].

Moreover, inborn errors of copper imbalance result in either Menkes disease or Wilson disease, which are genetically due to a mutation in copper transporter proteins, ATP7A or ATP7B, respectively [36, 37]. ATP7A deficiency in Menkes disease inhibits the export of intracellular copper, which subsequently restricts cupric incorporation into associated cuproenzymes, resulting in a state of copper deficiency [38]. Symptoms of Menkes disease appear in newborns at the age of 2-3 months manifested with seizures and hypotonia, prematurity and hypothermia, chronic diarrhea and lack of weight gain [36]. In contrast, pathogenic variants in the ATP7B protein in Wilson disease leads to defective transport of copper from the liver into bile, resulting in copper accumulation in the liver and/or brain [36, 37, 39]. Patients with Wilson disease present with liver symptoms generally between 8 and 20 years of age. In the second or third decade they can develop neurological symptoms, marked by bilateral greenish brown Kayser-Fleischer rings in the corneas due to copper deposition [40, 41].

Clinical Assessment of Copper Disorders:

Proper assessment of copper status requires an evaluation of various biomarkers. Copper deficiency can be clinically assessed by measurement of serum copper and ceruloplasmin concentrations, complete blood counts and bone radiographs, as well as inflammatory markers [22-25]. Since more than 90% of serum copper is bound to ceruloplasmin, their levels are proportional. An increase in concentration of non-ceruloplasmin bound copper (free copper) is a diagnostic test for Wilson disease [42]. However, the interpretation should combine all the laboratory results and clinical manifestations [43]. This is because in cases other than Wilson disease, such as acute liver failure and chronic cholestasis, free copper can also be elevated [44]. Free copper can be calculated using the formula below [45]:

Free copper = Total serum copper (µg/L) ─ ceruloplasmin-bound copper (µg/L)

ceruloplasmin-bound copper = 3.15 × ceruloplasmin (mg/L)

In newborns, reduced levels of serum copper and ceruloplasmin can non-specifically suggest Menkes disease. Based on the reduced activity of copper-dependent enzyme dopamine-β-hydroxylase in Menkes disease, a more specific and promising test was introduced by measurement of neurochemicals (catecholamines and their metabolites) in plasma [46]. Laboratory results for diagnostic

differentiation of copper disorders are summarized in the Table below (adapted from https://www.labcorp.com/test-menu/23121/copper-serum-or-plasma).

Treatment of Copper Imbalance:

Nutritional copper deficiency is improved following an adequate copper supplementation [26, 47, 48]. Hematologic symptoms of severe copper deficiency induced by gastric bypass surgery can be resolved following intravenous and oral copper supplementation; however, neurological symptoms may be only mildly improved [49]. Prolonged parenteral nutrition in copper deficient infants can induce cholestasis and therefore, management of copper deficiency in this population needs more careful consideration and consistent monitoring of serum copper concentration [25]. Administration of oral zinc or copper chelating agent penicillamine has been a standard treatment plan for Wilson disease. In cases of Menkes disease, it is crucial to start treatment in the first few months of life, as the neurological symptoms can be irreversible.

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Table 1: Copper deficiency laboratory assessment

Test	Acquired copper deficiency	Menkes Disease	Wilson Disease	Copper toxicity	Smoking, pregnancy, inflammation, estrogens
Copper, serum free	Low	Low	Low or normal	High	High
Ceruloplasmin	Low	Low	Low or normal	Normal or high	High
Copper, urine	Low	High	High	High	Normal
Copper, liver	Low	Low	High	Normal or high	Normal

Interview with a Distinguished Colleague

By Alison Woodworth, PhD

David G. Grenache, PhD, DABCC, FAACC

Chief Scientific Officer, TriCore Reference Laboratories, Albuquerque, New Mexico, USA

Congratulations on being elected to serve as AACC President in 2020 – 2021! What initiatives/programs are you most excited to implement or enhance during your time in office and will any affect the pediatric and maternal fetal laboratory medicine community?

One initiative I'd really like to get moving and incorporated into AACC's long term strategy is the value proposition of the clinical lab. This will affect not only the PMFD but the entire lab medicine industry. We all know that the value of lab testing in patient care is unquestionable. But clinical lab testing is increasingly being viewed as a mere commodity with value being placed on cost per test rather than where value needs to be place: the essential contributions to quality patient care and, from an economic perspective, simultaneously decreasing the total cost of care. I want to see AACC develop programs and services that help its members achieve these important goals and I think there are a few ways to accomplish them such as promoting and teaching laboratory stewardship, develop ways that we can demonstrate the value of lab tests within health systems, challenge the perceptions of the clinical laboratory as merely a provider of test results to a provider of integrated and actionable clinical insights. These activities will require us to recalibrate how we think of our own contributions to healthcare delivery. Existing programs I'd like to enhance and advance are AACC's Global Lab Quality Initiative that brings together international laboratory science experts to foster a global exchange of clinical testing best practices. This has been incredibly successful in the Caribbean and Central and South American and recent expansions into Asia also demonstrate its effectiveness. Along those lines, I wish to work with our member and staff leadership to increase AACC's efforts to promote the professional development of laboratory professionals in resource-limited countries with cost-effective programs that maximize benefits to recipients.

You have recently inspired the AACC community to embrace Lab 2.0. How will laboratory medicine change with this transition and how can members of the Pediatric and Maternal fetal laboratory medicine community be prepared for these changes?

I tend to think of the Clinical Lab 2.0 movement as a call for an evolution in laboratory medicine rather than a change. The generation of high quality clinical lab test results is not going away. Indeed, it's the foundation on which the concepts of Lab 2.0 rest. But while the transactions of lab testing aren't going away, healthcare delivery is changing from a fee-for-service commodity to a shared risk, value-based business. Lab professionals need to prepare for these changes now and that's where the evolution to Lab 2.0, comes in. It's about demonstrating the value that lab services deliver to drive better outcomes for patients, providers, and payers. Members can and should prepare for these changes sooner rather than later. Consider ways in which you can leverage the huge amounts of longitudinal lab data to which you already have access. For example, providing a longitudinal view of a patient's results relative to appropriate reference intervals can allow for early recognition of conditions, such as pre-diabetes or acute kidney injury, thereby slowing or preventing disease progression.

Another example is identifying gaps in care. While we often talk about managing over-utilization of lab tests we also need to appreciate under-utilization: tests that should be performed but aren't. Consider patients with diabetes or chronic kidney disease. Practice care guidelines are rather clear on how frequently tests associated with these conditions should be performed. Gaps in care occur when such tests aren't performed when they should be. Importantly, CMS has directly linked reimbursement for healthcare services to patient outcomes. With our access to real-time laboratory data, we can quickly identify patients who have gaps in care and thereby help managed care organizations achieve specific performance measures as defined by HEDIS (Healthcare Effectiveness Data and Information Set). These activities have real value, and dollars, associate with them. I can think of no better way to demonstrate the value proposition of lab medicine than this.

One focus you've had in your (relatively) new role at TriCore is population health. How will these types of population health initiatives affect the PMF laboratory medicine?

I really appreciate this question. As a regional laboratory network serving most of New Mexico, TriCore is truly leading the pack when it comes to leveraging laboratory data to improve the health of the population it serves. Our first concerted effort in the Lab 2.0 arena was focused on pregnant patients. We developed a prenatal dashboard, developed in consideration of prenatal care guidelines from the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics that allowed us to identify, in real-time, pregnant patients who have optimal care, gaps in care, risk factors, or both gaps and risk factors. In a pilot study we did with Medicaid patients enrolled with Blue Cross Blue Shield of New Mexico, we demonstrated that insights derived from our dashboard decreased the rate of preterm delivery and the number of NICU admissions. We were also able to help the payer achieve specific HEDIS measures such as timeliness and frequency of prenatal care. We are in the process of writing up this pilot study and are really excited about it because it's a strong demonstration of Clinical Lab 2.0 in action. What we're doing here in New Mexico is something any lab system can adopt and implement. It's just a matter of getting started.

Excerpts from the Literature

Kelly Doyle, PhD, DABCC, FAAC, Clinical Chemist, Intermountain Healthcare, Salt Lake City, UT, USA

What Is House Bill HR 1318 and Why Should Clinical Laboratorians Know About It?

What is it?

House Bill H.R. 1318 – Preventing Maternal Deaths Act of 2018 (formally 2017) was recently signed into law on December 21, 2018.[1] This new law allows for Health and Human Services to provide grants to individual states for use in organizing review committees tasked with tracking and documenting of pregnancy-related and pregnancy-associated deaths. It is hoped that this data will enable state health departments to disseminate findings and improve health care provider education as well as to contribute to national data and efforts to mitigate maternal deaths nationally.[2]

Why is this happening?

The US has one of the highest rates for pregnancy-related maternal deaths among developed nations.[3] Leading causes for pregnancy-related death include hemorrhage, cardiovascular conditions, cardiomyopathy, infection, embolism, mental health conditions,

and preeclampsia/eclampsia; while incidence is tied to multiple variables including age, race, state, and stage of pregnancy.[4] While the federal government has been slow to respond to this health issue, many states recognized the need for review committees aimed at tracking and understanding maternal deaths and have been operating for nearly 100 years.[4] In fact, nearly two-thirds of states currently have review committees and actively collect data. However, while these committees have historically functioned on independent governance and funding, philanthropic efforts such as the Merck for Mothers campaign by the pharmaceutical giant Merck in conjunction with the Safe Motherhood initiative within the Centers for Disease Control and Prevention (CDC) are taking a role in standardization and funding[5]. Internationally, the Worldwide Health Organization (WHO) introduced the Maternal and Perinatal Death Surveillance and Response (MPDSR) with a guideline in 2013 and has shown that surveillance does aid in mitigating maternal deaths.[5] Essentially, H.R. 1318 aims to fund a standardized data collection process across states and enable data sharing between committees.

Why is this important to you?

Often the etiology of pregnancy-related deaths is related to medical conditions wherein laboratory tests are utilized to make diagnoses, provide care, and to monitor treatment. CDC estimates that nearly 60% of maternal deaths are preventable but signs and symptoms often go unnoticed or are not acted on quickly enough[4]. NPR's extensive coverage and reporting on maternal deaths in the US highlight many cases of women who felt like something was amiss with their health but provider inaction, poor communication, and absent protocols were common themes in the reports of maternal death across the US.[6]

What can laboratories do to help?

In a 2017 report from a group of maternal mortality review committees, they classified critical factors attributed to maternal deaths as patient-, provider-, and systems of care-specific. For instance, in describing deaths attributed to hemorrhage, each of these areas of critical factors were determined near equally culpable. Patient-specific causes were attributed to mothers not being aware of the warning signs to alert the providers, whereas provider- and systems of care-specific causes were related to delay in diagnosis, inadequate training, and lack of coordination in patient management. In contrast, death due to preeclampsia and eclampsia were attributed predominately to provider- (62.2%) and system of care-specific (16.2%) causes such as misdiagnosis, inadequate assessment, and lack of communication between providers.[4]

Laboratory likely fits best within the category of system of care and shares the responsibility of communication and coordination of care with providers. For any one provider, these cases may be uncommon or rare events. How can the laboratory provide value to expectant or new mothers and their providers? Would there be utility in establishing order sets for conditions like preeclampsia or HELLP syndrome so providers can readily get the lab tests that are needed without hunting through the lab test directory? What about the possibility of delta checks, critical alerts, or resources on our lab websites for proper test ordering? Often order sets are outside of our influence but perhaps we can start conversations or be at the table with our maternal health colleagues to discuss ways in which we can provide value. If you already have coordinated efforts or protocols in place, please share what you are doing on the Artery!

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2018 PMF Division Executive Board:

Welcome to our new Members At Large: Jane Dickerson and Amy Karger!

Thank you for your service: Joely Straseski and John Mills!

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