Noninvasive Anemia Screening

Technology Opportunity Assessment

Prepared for the Merck for Mothers Program
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Summary

Anemia can reduce a woman’s ability to withstand the adverse effects of blood loss during and after pregnancy. Noninvasive anemia screening devices have been designed to make it easy to monitor a pregnant woman’s iron levels to help reduce her risk of potentially life-threatening complications during or shortly after childbirth as well as preventing long-lasting health problems associated with severe anemia.

Statement of Need

Obstetric hemorrhage is estimated to cause 25% of all maternal deaths and is the leading direct cause of maternal mortality worldwide. Postpartum hemorrhage (PPH), defined as vaginal bleeding in excess of 500 mL after delivery, is generally considered to account for a majority of the cases of obstetric hemorrhage, occurs in over 10% of all births, and is associated with a 1% case fatality rate. Although active management of the third stage of labor can prevent up to 60% of PPH cases, PPH continues to have devastating impact on women in resource-poor settings where home births are common and hospitals or health facilities are often inaccessible. Obstetric hemorrhage accounts for 34% of maternal deaths in Africa, 31% in Asia, and 21% in Latin America and the Caribbean, while only 13% of maternal deaths in developed countries are due to hemorrhage. Additionally, if women do survive PPH, approximately 12% will have severe anemia, and if women survive severe PPH (greater than 1,000 mL of blood loss) (“near misses”), they are significantly more likely to die in the year following the PPH.

Anemia continues to be one of the most serious global health problems, with far-reaching consequences for human health as well as social and economic development. It is estimated that iron-deficiency anemia (IDA) affects more than one billion people worldwide. Anemia particularly affects pregnant women and young children in developing countries. IDA in children has been associated with impaired cognitive performance, motor development, coordination, and language development. In developing countries, 42% of children less than 5 years of age and 53% of children from 5 to 14 years of age are anemic. For women, the numbers are alarming: 56 million pregnant women and 468 million nonpregnant women suffer from IDA. The majority of these women live in Africa and Southeast Asia. IDA places pregnant women at risk for poor pregnancy outcomes including increased risk of maternal and perinatal mortality and morbidity, preterm births, and low-birth-weight babies.

While a recent study has shown that maternal mortality declined by one-third between 1990 and 2008, 350,000 women in developing countries still die every year from pregnancy-related complications. A majority of these deaths are caused by PPH, and the risk of dying depends not only on access to emergency care but also on the amount of blood loss and on the health status of the women. Women who
suffer from anemia are less able to withstand the adverse effects of excessive blood loss and are more susceptible to infection, fatigue, and depression. Furthermore, a study conducted by Kavle, et al. provides evidence of the link between anemia during pregnancy and increased likelihood of blood loss during and after delivery, thereby increasing the woman’s risk of PPH and the subsequent mortality and morbidity risks. A pre-pregnancy store of more than 500 mg of iron is required to avoid iron deficiency during pregnancy, yet these levels of iron are only present in 20% of menstruating women in developing countries before the start of their pregnancy. Current World Health Organization guidelines for antenatal care recommend universal iron-folic acid supplementation with a minimum of 90 days of supplementation for pregnant women where anemia is widespread. However, many countries do not meet these standards, many pregnant women do not attend antenatal care in the first trimester, and coverage remains low.

To effectively tackle anemia and reduce related mortality and morbidities would require addressing the root causes of anemia including poverty, illiteracy, malnutrition, and disease (specifically malaria and helminthes). Intermediate measures such as strengthening supply and distribution channels for iron pills, targeted food fortification programs, community education, effective screening, and monitoring programs should be a priority if the detrimental consequences of IDA on maternal and newborn health are to be curtailed. Countries such as Thailand and Nicaragua have been effective in combating micronutrient deficiencies through a well-planned and -executed strategy of iron supplementation, food fortification, monitoring, and behavior change communication. However, in most developing countries, preventive interventions such as iron supplementation, food fortification, malaria treatment, and deworming while effective are widely underutilized. In these cases, effective screening and monitoring becomes even more important.

Moderate anemia is treated by iron supplements and improved nutrition; severe anemia, however, often requires more resource-intensive and riskier emergency interventions such as blood transfusions. Prenatal programs in most developing countries dictate that women should be given iron supplements, counseled, and monitored for anemia. In reality, many health programs lack iron supplies, women who are already moderately anemic need more than the minimal amount of iron the supplement provides, and cultural taboos around food during pregnancy affect the effectiveness of current approaches. Because of the combination of these factors, early detection, monitoring, and treatment of anemia of pregnant women is critical for appropriate tailoring and targeting of the interventions to serve the population’s needs.

Effective screening programs for IDA in prenatal and postnatal programs have been hampered by the lack of simple, safe, accurate, low-cost hemoglobin testing tools. The majority of women who suffer from anemia live in low-resource areas where accurate diagnostics are unavailable. In such settings, anemia often goes undetected and untreated. A noninvasive device offers major advantages over current methods and approaches and would expand access to screening and increase early identification and treatment of anemia.
Low-cost, noninvasive anemia screening tools would bring positive, radical change to anemia screening and monitoring and support effective treatment practices.

Technology Solutions Landscape

Most IDA screening tests are generally difficult to use, especially in rural settings. The most commonly used methods—the Sahli method, the color scale, and clinical assessment—have limited sensitivity and are most commonly used in low-resource health settings to diagnose the most severe cases of anemia. These methods rely on subjective interpretation. Other, more quantitative point-of-care tests such as the HemoCue® require blood samples, maintenance of equipment, and recurrent supplies, limiting their use in resource-poor settings. The commonly used laboratory-based methods are expensive, complex, and necessitate a blood draw, requiring a trained technical person.

Generally, the four most important factors that have a significant impact on the adoption of a technology are existing infrastructure, cost, accuracy, and distribution. Which anemia screening tests are chosen at each level of the health system will depend on the resources available at each facility and how the three core benefits—accuracy, ease of use, and cost—are prioritized. Generally, primary health care settings aim for tests that are easy to use and lower cost because they do not have highly trained staff or the resources needed to support expensive, more accurate, and complicated tests. They may have to compromise on screening test accuracy because of these constraints. On the other hand, tertiary care facilities require highly accurate screening tests because they function as referral centers and handle complicated cases. These facilities are more likely to have highly trained staff and greater resources; therefore, ease of use and costs of tests are not their highest priority when they consider which test to use.

Attempts to develop more accurate, easier-to-use, and sustainable anemia screening technologies have been ongoing for many years. Noninvasive technologies have been of special interest, and with recent advances in technology and expertise and continued concern about the risks of blood-borne diseases, there have been renewed efforts among researchers and manufacturers to develop such technologies. A noninvasive device would eliminate the need for a blood draw, the use of costly consumables, the disposal of hazardous waste, and the subjective nature of many of the currently available tests. It could potentially improve clinical practice by expanding access to screening among high-risk populations at the periphery and in more remote locations, providing immediate quantifiable measurements to guide and support early treatment and monitoring and facilitating surveillance and monitoring efforts.

Several promising technologies designed for use at point of care by non-laboratory-trained health care providers in developing countries have emerged:

- Pronto-7™ developed by Masimo Corporation (Irvine, CA).
- TouchB developed by Biosense (Mumbai, India).
• Haemospect® developed by MBR Optical Systems GmbH & Co. KG. (Germany).
• NBM-200 developed by OrSense (Israel).

All devices use a finger probe and technology analogous to noninvasive pulse oximetry to provide a quick spot check for total hemoglobin. These technologies address many of the problems that faced previous noninvasive devices: they are smaller in size, more compact, simple to use, and provide immediate results. Some have the added advantage of providing simultaneous measurements of hemoglobin, oxygen saturation, and pulse rates, thus increasing the impact and applicability of these tools well beyond anemia screening and control programs to a wider range of programs affecting the health of women.

The Pronto-7™ by Masimo Corporation

The Masimo Pronto-7™ is a handheld portable device for spot checking of total hemoglobin. Three measurements are displayed simultaneously on a screen: a total hemoglobin value in grams per deciliter, an oxygen saturation rate, and a pulse rate. The results on the screen are available within 40 seconds. A perfusion index is displayed during the 40 seconds, providing the health care worker with feedback in case of low perfusion, which could lead to failure of the device to give a hemoglobin value. The device can save patient data for trending. It also has the capacity to average out three readings in cases where either perfusion is low or the health care provider has some question about the values displayed and prefers to repeat the test. The device comes with a one-year warranty. Masimo generally estimates the lifetime of handheld devices to be about five years before they need to be replaced.

The Pronto-7 components consist of the device, batteries, power cords, adapters, and the set of probes (one child and one adult probe). The adult probes come in three sizes: small, medium, and large. A laminated-paper sizing tool attached to the device cord helps determine the adult probe size required. The child probe comes in one size and is designed for children over 10 kg. An infant probe is currently in development. The probes are pre-loaded with 360 tests. Masimo estimates that the sensor can perform up to 10,000 tests before it needs replacement. The Pronto-7 comes equipped with a rechargeable battery that will last for up to 2 hours of continuous testing, or about 140 tests. The price of the device in developed- and emerging-country markets is largely dictated by the medical reimbursement schemes.

The Masimo Pronto-7 is approved by the US Food and Drug Administration and has the CE mark for total hemoglobin detection. It is on the market in high- and middle-income countries and is used widely at the point of care in private clinics. Limited use of the device has been reported in private settings in developing countries, but it is not clear where the device is being used. Performance and acceptability studies were conducted in Guatemala, India, and South Sudan. Results from the performance and acceptability study in South Sudan are not yet published. A clinical accuracy and feasibility study will take place in Ghana in 2013. Modifications have already been made to the device based on preliminary results from the field, and further form-factor changes are anticipated to make the device more adapted to the conditions of low-resource settings.
The TouchHb by Biosense

The Biosense TouchHb is a handheld portable device that provides a hemoglobin reading in grams per deciliter. The value appears on a display screen within 32 seconds. The TouchHb device comes equipped with a finger probe and AA batteries. The probe is estimated to last for about 3,000 uses. A user assessment of the TouchHb device was conducted in India with nurse midwives working in primary health care centers. Modifications to the device and alternative display options are being considered as a result. The TouchHb technology is currently being introduced in India on a small scale as the company gears up for large-scale production. The design team at Biosense is investigating the possibility of making the device compatible with an android-based mobile phone. Design and development work have been funded largely through various grants and awards such as the Echoing Green award, a grant from Villgro, and support from the department of Biotechnology in India.

The NBM-200MP by OrSense

OrSense’s NBM-200MP is a device that noninvasively and continuously monitors and displays total hemoglobin, oxygen saturation, low-signal oximetry, pulse rate, and plethysmography. The system is designed for use in hospitals, including operating and recovery rooms and intensive care units, as well as in outpatient sites and emergency services. The technology was validated on over 4,000 patients and blood donors at over 15 sites in the United States and Europe. OrSense’s noninvasive hemoglobin monitor has CE certification. The NBM-200MP is battery operated and composed of a monitor and a sensor. The current configuration has 5,000 tests per sensor.

Haemospect® developed by MBR Optical Systems GmbH & Co. KG. and distributed by STRATISmed

MBR Optical Systems GmbH & Co. KG. developed the Haemospect® for the noninvasive measurement of hemoglobin. It is a handheld portable device that was originally designed for continuous measurements of six key indicators. Individual point-of-care measurements are now possible with the device. The device is powered by batteries and uses a button sensor that adheres to the palm side of the finger and displays total hemoglobin, oxygenated hemoglobin, deoxygenated hemoglobin, water content given in percent per gram of tissue, volume of hemoglobin in tissue, and capillary measurements. The device was designed for developed-country hospital and emergency settings. Only one assessment of the device in low-resource settings has been reported in Guatemala. It is unclear if further assessments in resource-poor settings have been conducted.

Of the three technologies that are commercialized, the Pronto-7 is most likely in the more advanced stage of development and investigation for resource-poor settings. It is also the simplest of the three technologies. It is being tested in developing-country settings for acceptability, usability, and accuracy. Further studies and pilot demonstration projects involving the technologies should be conducted to build evidence and evaluate the operational feasibility of introducing these technologies into maternal health programs.
Gap Analysis

Maternal anemia continues to be a major problem, and effective ways to address the problem globally have not been very successful. A safer, easy-to-use, and accurate screening device is one component of an effective program to successfully combat anemia. However, lingering issues remain, and more information is needed to address the following questions:

- What changes need to be made to the current devices to make them more suited for developing-country settings? Operational studies to assess the acceptability and usability of the noninvasive devices need to be conducted in low-resource settings.

- What level of accuracy is required from a noninvasive device? Is a +/- 1–2g/dl margin good enough? Studies evaluating the noninvasive devices against a gold standard and comparing them to the HemoCue device will be needed to determine the level of accuracy of the devices in resource-poor settings and the implications for program introduction. A validation study that will compare the Pronto-7 to the HemoCue and a hematology analyzer, as the reference method, will start in June 2013 in Ghana, in collaboration with one of the affiliated research centers of the Ghana Health Services.15

- The noninvasive screening technology has some limitations that need to be understood and addressed in order to ensure high accuracy and reduce device failure modes. The most dominant limitation is the ability of the devices to assess hemoglobin when perfusion is low. Masimo has included a perfusion index in their device, but more needs to be done to mitigate that condition or offer ways for providers to anticipate the possibility that the device cannot provide a hemoglobin reading, and plan for alternative ways to screen the patient. Other conditions such as high levels of bilirubin, hemoglobinopathies, skin tones, and motions also may affect readings.20

- Another key question that deserves some attention is in what way will a noninvasive hemoglobin screening technology which presents major advantages over current screening approaches change practices in a way that will have a major impact on health outcomes? Will the introduction of a noninvasive device empower health workers? Offer more opportunities for community outreach and counseling? Allow earlier identification of high-risk women? Tailor interventions and treatments more effectively? Target supplementation in a more cost-effective and efficient approach?

- How cost-effective is a noninvasive hemoglobin screening technology? Would it be more cost-effective to focus on supplementation programs by strengthening logistics and distribution systems? It would be useful to look at the effectiveness of screening using noninvasive devices and how they might change outcomes.
Investment Opportunity

Further investment is needed to support continued development, technology optimization, validation, commercialization, and scale-up of noninvasive anemia screening devices. A recommended scope of work is outlined below.

**Conduct multi-country and multi-site validation studies.** The goal of these studies would be to assess the accuracy and acceptability of noninvasive anemia screening devices in developing-country health facilities. The World Health Organization recommends that hemoglobin measurement devices come within +/-1 g/dL of the gold standard defined as a hemoglobin reading obtained from an automated hemolyzer. The studies will assess the noninvasive device’s hemoglobin readings and compare them to hemoglobin tests run on a qualified hemolyzer. The noninvasive device will also be compared to point-of-care hemoglobin screening tests currently in use. This is most likely to be either the HemoCue or the Sahli test. The studies would focus on India (sites in 2–3 states) and at least two countries in sub-Saharan Africa (possibly Ethiopia, Tanzania, or Ghana). The key questions addressed in the studies would be the following:

- How accurate is the device?
- How well does it adjust to varying conditions/factors such as skin tone, environmental variations, finger calluses, testing set-up (space, motion, jostling)?
- What are the observable causes of device failure?

**Conduct multi-country and multi-site introductions of the noninvasive device in antenatal programs.** The introduction activities should aim to accomplish the following:

- Create demand by investing in introductions and evaluations of the noninvasive devices in two to four countries through broad collaborations with ministries of health, nongovernmental organizations, and other key stakeholders. Country guidelines, protocols, and policies should be discussed and modified as needed.

- Establish the value proposition of the noninvasive anemia screening technology through a series of studies that will analyze the impact of the device on maternal anemia programs, PPH programs, malaria control, and other efforts, based on country-specific indicators and process outcomes. The following health outcome indicators should be collected and analyzed: numbers of women identified with moderate to severe anemia in the antenatal and postpartum periods, preventative/therapeutic measures taken, increases in iron supplements distributed, increases in follow-up visits, numbers of referrals, emergency management plans, number of transfusions ordered, number of infusions given, and changes in treatment approaches. Health system outcome indicators to identify potential barriers to wide-scale adoption should also be collected and analyzed.
• Plan for scale-up through a series of activities including an advocacy and communication plan, strengthening of supply and distribution chains, and linking with other health and nutrition programs.

Conduct a market study focusing on India and one to two countries in sub-Saharan Africa. The following activities should be carried out to further strengthen the value proposition of noninvasive hemoglobin measurement devices for maternal health.

• A cost-effectiveness study should be completed, focusing particularly on moderate and severe anemia and the impact of the noninvasive devices on the early identification of women at high risk and the efficacy of their clinical management.

• Investigate the feasibility of expanding the reach of the technology through the following actions:
  o Look at market potential in both the public and private sectors.
  o Assess whether the oxygen saturation and pulse rate measurements that the Pronto-7 provides simultaneously with hemoglobin can be used by maternal health programs to further identify at-risk women.
  o Assess whether the current device model can be modified to allow for noninvasive measurement of other disease markers such as malaria, diabetes, and hypertension.
References


