STILLBIRTH WORKING GROUP OF COUNCIL MEETING SUMMARY

January 24, 2024 (Virtual)

Contents

Working Group Members

Present
Co-Chairs
Lucky Jain, M.D., Emory University
Uma M. Reddy, M.D., M.P.H., Columbia University Irving Medical Center, representative of the American College of Obstetricians and Gynecologists

Members
RADM Wanda D. Barfield, M.D., M.P.H., Centers for Disease Control and Prevention (CDC)
Alison Cahill, M.D., MSCI, University of Texas at Austin
Ada Dieke, Dr.P.H., M.P.H., CDC
Donald Dudley, M.D., University of Virginia
Andrew Fullerton, M.P.P., March of Dimes
Karen Gibbins, M.D., MSCI, Oregon Health & Science University
Katherine Gold, M.D., M.S.W., M.S., University of Michigan
Debbie Haine Vijayvergiya, The 2 Degrees Foundation
Isabelle Horon, Dr.P.H., CDC
Stephanie Leonard, Ph.D., Stanford University
Monica Longo, M.D., Ph.D., Eunice Kennedy Shriver National Institute of Child Health and Human Development
Mana Parast, M.D., Ph.D., University of California (UC) San Diego
Tina Pattara-Lau, M.D., Indian Health Service
Jennifer Reefhuis, Ph.D., CDC
George Saade, M.D., Eastern Virginia Medical School
Mikyong Shin, Dr.P.H., M.P.H., RN, CDC
Robert M. Silver, M.D., University of Utah Health Sciences Center, Representative for Society for Maternal–Fetal Medicine
Catherine Vladutiu, Ph.D., M.P.H., Health Resources and Services Administration (HRSA)
Maeve Wallace, Ph.D., M.P.H., Tulane University School of Public Health
Ronald J. Wapner, M.D., Columbia University
Jill Wieber Lens, J.D., University of Arkansas School of Law
Monica H. Wojcik, M.D., Boston Children's Hospital

Absent
Joanne Cacciatore, Ph.D., M.S.W., Arizona State University
CAPT Amanda Cohn, M.D., CDC
Cynthia Gyamfi-Bannerman, M.D., M.S., FACOG, UC San Diego School of Medicine
Carol Hogue, Ph.D., Emory University
Denise Jamieson, M.D., M.P.H., Emory University
Jenna Nobles, Ph.D., University of Wisconsin–Madison

Others Present
Speakers
NICHD Staff Members
Members of the Public

Call to Order

Natasha H. Williams, Ph.D., J.D., L.L.M., M.P.H., Legislation and Public Policy Branch, NICHD

Dr. Williams opened the meeting at 9 a.m. ET and welcomed the attendees. She made the following announcements:

- The meeting was being recorded, and the videorecording would be available on the NIH VideoCast website.

- Having an NICHD grant or applying for future NICHD funding would not constitute a conflict of interest for Working Group (WG) members, because no funding-related matters would be discussed during this meeting.

- Members of the public who had registered for this meeting would be able to submit questions via web form.

Welcoming Remarks

Diana W. Bianchi, M.D., Director, NICHD

Dr. Bianchi greeted the participants and introduced herself.

Stillbirth, she said, is a tragedy that strikes more than 20,000 families every year in the United States. NICHD is committed to research aimed at reducing stillbirths, which disproportionately affect women who are non-Hispanic Black, American Indian and Alaska Native, and Native Hawaiian and Pacific Islander.

Dr. Bianchi also highlighted efforts to develop diagnostics through the Rapid Acceleration of Diagnostics Technology program—specifically the fetal monitoring challenge. Up to $2 million in prizes is being offered to develop a device that directly assesses one or more measures of fetal health during the late antepartum and/or intrapartum periods of pregnancy. Dr. Bianchi said that 10 innovators were selected as the winners of Phase I. They will now move on to Phase II, which includes a demonstration—an opportunity to showcase their device and share their plans for further development—at an event on January 30, 2024, on the NIH campus. The innovators will be competing to advance to Phase III, the technology development sprint.

Dr. Bianchi presented the agenda for today's meeting. She also explained that the WG's preliminary findings will be presented to the National Advisory Child Health and Human Development (NACHHD) Council during its meeting on June 3–4, 2024.

In closing, Dr. Bianchi thanked the WG co-chairs, Dr. Jain and Dr. Reddy, for their leadership. She also recognized the WG members for their time and insights and acknowledged the day's speakers for bringing their expertise to bear on the serious issue of stillbirth. Finally, she thanked the NICHD personnel and logistics staff for supporting the meeting and expressed her gratitude to the families who have shared their experience of stillbirth to advocate for better pregnancy outcomes in the future.

Remarks by WG Co-Chairs

Lucky Jain, M.D., Co-chair, Emory University School of Medicine, Department of Pediatrics

Uma Reddy, M.D., M.P.H., Co-chair, Columbia University Irving Medical Center; Representative, American College of Obstetricians and Gynecologists (ACOG)

Dr. Jain thanked Dr. Bianchi and NICHD for supporting research aimed at reducing rates of stillbirth. The hope is to lower the rate of stillbirth in the United States, with the eventual goal of lowering it globally. Dr. Jain reviewed the charge to the WG, which is to identify the following:

- The state of current knowledge on stillbirth and prevention

- Areas of improvement for data collection

- Current resources for families affected by stillbirth

- Next steps to gather data and reduce rates of stillbirth in the United States

Dr. Jain presented a list of WG members who together represent a broad spectrum of clinical and scientific expertise. Everyone has participated in the proceedings, including helping to create the group's first report, in 2022. The plan is to prepare a second report later this year.

Dr. Reddy said that the meeting speakers are exceptional in their fields and are now applying their expertise to address stillbirth. Excellent progress has been achieved in some parts of the world. She introduced the opening speaker, Prof. Smith, and highlighted some of his major accomplishments.

Opening Speaker: Strategies for Predicting Risk of Pregnancy Complications and Reducing Stillbirths

Gordon Smith, M.D., Ph.D., D.Sc., FRCOG, FMedSci, University of Cambridge, U.K.

Prof. Smith opened his presentation with the story of Sophie, a healthy first-time mother who experienced fetal demise at 36 weeks of pregnancy. Baby girl Liberty was stillborn 2 days after labor was induced. An autopsy did not reveal any structural or genetic abnormalities, but because of idiopathic intrauterine growth restriction, at 1.45 kg, Liberty was about half the size she should have been for her gestational age.

Prof. Smith explained that Sophie's pregnancy was managed per guidelines, which recommend monitoring fetal growth by measuring fundal height externally with a tape measure. Up to half of stillbirths are related to fetal growth. Based on evidence from eight randomized controlled trials (RCTs) in which a total of 35,000 women were enrolled, routine pregnancy ultrasound offers no advantage over fundal height measurement as a way to reduce fetal mortality.

Prof. Smith said that stories like Sophie's have driven the search for better methods to monitor fetal growth and predict pregnancy complications linked with stillbirth. There is also interest in conducting RCTs to evaluate novel methods for screening and interventions. The overall strategy in U.K. research focuses on women's first pregnancies because they have a higher rate of complications, and there is no history of prior pregnancy outcomes for clinicians to use in risk assessment. Prof. Smith also pointed out that research is focusing initially on predicting complications at term because induction of labor is a relatively safe and effective intervention in that time frame. Another key concept underpinning research is the need to carry out noninterventional prospective cohort studies to assess diagnostic test accuracy before attempting RCTs. Prof. Smith pointed out that proof of principle for screening interventions is generally more informative if randomization occurs after risk assessment.

Prof. Smith described research efforts in the U.K. to improve birth outcomes. The [Pregnancy Outcomes Prediction study](#) (POPs) was a prospective cohort study that enrolled 4,500 nulliparous women and generated a large, high-quality biobank; each specimen is backed up with extensive phenotypic data. The study yielded a trove of valuable publications, three of which provided a basis for a potential novel screening test at 36 weeks' gestation. The screening combines maternal risk factors, ultrasound exam, and measurement of placentally derived proteins in maternal serum. The screening was able to identify about 7% of nulliparous women who have a 50% chance

of a combined outcome of preeclampsia, fetal growth restriction (FGR), or neonatal morbidity.

A follow-on cohort project—POPs2, which includes a nested RCT of screening and intervention—is underway. The investigators aim to recruit 4,500 nulliparous women with singleton pregnancies who will undergo the experimental screening assessment during their 36-week visit. The estimated 7% of women who will be identified as at high risk will then be randomly assigned to either routine care or intervention (early delivery).

This study design will allow validation of the screening test by comparing outcomes for high-risk women who receive routine care to outcomes for women who screen as low risk. Comparing outcomes for high-risk women who receive routine care with outcomes for women who have an intervention will allow the researchers to determine whether intervening mitigates risk.

Prof. Smith explained that the screening includes use of an autoanalyzer to determine the maternal ratio of sFLT-1 (soluble fms-like tyrosine kinase 1) to PlGF (placental growth factor) in maternal serum. The sFLT1 binds to and inactivates PlGF in the maternal circulation. An elevated sFLT1-to-PlGF ratio is predictive of preeclampsia. The ratio is currently used by the U.K.'s National Health Service and the European Union to rule in or out preeclampsia when it is clinically suspected. Evidence also suggests that the ratio is predictive of preeclampsia and FGR without clinical signs; hence, it has potential utility as a screening test.

Prof. Smith said that there is a compelling need for biomarkers that can predict stillbirth and FGR. The sensitivity of combined ultrasound and the sFLT1-to-PlGF ratio for FGR is low—about 40%—most likely because FGR is the endpoint of multiple physiologic pathways and the sFLT1-to-PlGF ratio is specific for one subtype of FGR. That means that it would be possible to prevent only a minority of cases. One research aim is to identify predictive markers of other subtypes of FGR.[1]

Prof. Smith then described the Wellcome Leap program. One objective of the program is to harness the power of omics in the effort to predict pregnancy outcomes and reduce stillbirths. Instead of focusing on a particular pathway or target molecule, these platforms test for a category of biological molecule across multiple pathways and processes. Such methods are ideal in situations where a detailed mechanistic

---

[1] Smith, G. C. S. (2021). Developing novel tests to screen for fetal growth restriction. *Trends in Molecular Medicine, 27*(8), 743–752. https://doi.org/10.1016/j.molmed.2021.05.006.

understanding is lacking. For the program, the goal is to test maternal serum samples using the proximity extension assay to comparatively quantify levels of about 3,000 proteins through extension and sequencing of very small samples. This technique is particularly well suited for clinical translation because multiple companies already market antibody-based assays in pregnancy. Clinical tests can measure with very high correlation approximately 3,000 proteins in 6 µL of fluid.

The program aims to identify novel predictors of FGR, preeclampsia, gestational diabetes, and spontaneous preterm birth with the Olink Explore platform on 3,200 POPs samples using a case-cohort study design. Panels of predictive proteins would then be validated on external datasets. The investigators identified more than 600 samples of interest based on preeclampsia, preterm delivery, gestational diabetes, preterm birth, or FGR. More than 800 samples were available from 208 women whose infants were affected by FGR at term.

Prof. Smith said that comparing the levels of each protein in the FGR cases and in the controls presented a complex, Big Data analytic challenge that is common with omics methods. Making 3,000 comparisons increases the risk of chance findings, but this potential problem was overcome when large numbers of statistical tests were performed.

Examining the *p*-values for frequency counts revealed a signal of interest. Applying four "false discovery" statistical methods resulted in a total of 124 proteins of interest linked with subsequent delivery of an infant with FGR. The investigators are currently working with Olink on generating a 21-protein model using 28-week blood samples to predict term FGR. The model will then be validated against two external datasets. Further testing will be conducted with POPs2 samples.

In conclusion, Prof. Smith said that sFLT1-to-PIGF may have potential as a screening test in the near term, but omics methods offer great promise for predicting risk of FGR and preeclampsia—both of which are linked with stillbirth. The proximity extension assay proteomics approach has a particularly clear line of sight to translation based on its ability to identify robust targets.

Moderated Discussion

Monica Longo, M.D., Ph.D., NICHD

Question: Dr. Saade asked about the reliance on FGR and how it translates into a clinically significant outcome besides just a birthweight. For example, if FGR is less than the 30th percentile, would that be predictive of stillbirth?

Answer: Prof. Smith noted that stillbirth is rare, affecting only 1 or 2 births per 1,000. This means that RCTs would have to recruit hundreds of thousands of women to discern any differences due to an intervention. Therefore, proxies—conditions that allow the infant to survive but are strongly associated with stillbirth—are needed for RCTs. A birthweight less than the third centile at term is associated with an eightfold increase in risk of neonatal mortality; it also doubles the risk that a child will need special educational services later in childhood. Although FGR is a theoretical concept that lacks a gold standard, the third centile seems to be a reasonable proxy that captures some of the associations we are trying to prevent.

Question: Dr. Jain asked about the optimal timing in terms of pregnancy trimester for screening for PlGF or other angiogenic factors that might have predictive value in preeclampsia or in stillbirth occurrence.
Answer: Prof. Smith said that there is no point in having a screening test if there is no intervention. For example, there is the potential to cause harm with a false positive screening test done at 28 weeks' gestation or earlier in pregnancy due to delivery of a preterm infant. The risks of inducing labor are lower at 36 weeks, so it makes sense to perform screening then—when a relatively low-risk intervention is possible. Also, associations between biomarker findings and outcomes are much stronger when they occur closer to disease manifestation.

Question: Dr. Jain asked about the aim of the multi-omics platform assessment. Would it be amenable to point-of-care testing or even home testing?
Answer: Prof. Smith said that the COVID-19 pandemic clearly led to a shift in thinking about in-home testing, but he emphasized the importance of safety. With unrestricted point-of-care or home testing, one would have to be concerned about downstream effects, such as an epidemic of preterm births.

Question: Dr. Reddy asked whether routine third-trimester ultrasound exams are recommended.
Answer: Prof. Smith said that in the U.K., the recommendation is against performing routine ultrasound exams except for ascertainment of presentation. A study is now underway to learn whether midwives can use point-of-care ultrasound devices to check presentation to prevent undiagnosed breech birth. A small number of babies die of breech in the U.K. every year, and that seems like an avoidable tragedy. However, there is a risk of using routine ultrasound at 36 weeks for biometrics: (1) false-positive diagnosis of a large fetus that could lead to preterm delivery via unnecessary cesarean section, and (2) false-positive diagnosis of FGR that could lead to unnecessary labor induction. Either of these scenarios has potential lifelong consequences. In Prof. Smith's view, biometric analyses need a proper RCT to ascertain their predictive value.

He said that routine ultrasound to check presentation would probably be justified because a small number of infants die as a consequence of breech presentation. But ultrasound poses a risk if used for ascertaining fetal size.

Question: Dr. Reddy asked about the POPs2 risk assessment. What is the threshold for a positive screening test?
Answer: Prof. Smith said that women whose sFLT2-to-PlGF ratio is greater than 110 have a 50% risk for preeclampsia, and half of those cases would have preeclampsia with severe features. If the ratio is between 38 and 109, if the fetus is small for gestational age on scan, and if the mother has additional risk factors, then there is about a 50% chance of a bad outcome. Without other maternal risk factors, the risk drops to about 15% to 20%. Combining the sFLT2-to-PlGF ratio, ultrasound imaging, and maternal risk factors greatly increases the positive predictive value of the screening.

Question: Dr. Reddy asked about the role of ultrasound exams in POPs2.
Answer: Prof. Smith said that POPs2 is using ultrasound imaging just for research purposes, to detect certain anomalies or breech presentation. It is not used for estimating fetal size, because of the limitations of biometry.

Question: Dr. Reddy asked about early preterm stillbirths (before 36 weeks' gestation), which constitute the majority of stillbirths.
Answer: Prof. Smith said that the external validation study has modeled down to 28 weeks for FGR, but a very high positive predictive value needs to be achieved in that time frame to avoid generating many false positive results. High predictive values appear to be possible when the sFLT2-to-PlGF ratio is combined with ultrasound. But avoiding interventions in early stages of pregnancy is important.

Question: Dr. Parast asked whether Prof. Smith has considered maternal obesity or other conditions in combination with falling fetal growth (as opposed to the third centile) as a predictor of actual placental function.
Answer: Prof. Smith said that with the proteomics analysis, the definition of FGR is "birthweight less than the third centile" or "birthweight less than the 10th centile with reduced abdominal growth velocity." Both are included in the POPs2 definition of birth FGR.

Question: Dr. Longo inquired about the degree of correlation among FGR, ultrasound, and the biomarker.
Answer: Prof. Smith mentioned previous published work on metabolomics but said that it would not be possible to translate such tests into clinical use. No companies were

interested in trying to develop a test based on metabolites. Regarding ultrasound and proteomic biomarkers, Prof. Smith speculated that a combination of the two might be more predictive than either alone, though he has not done that analysis yet.

Question: Dr. Jain commented on Prof. Smith's work aimed at identifying the ideal gestational age for healthy delivery. Preventing early-term birth reduces potential risk, but how can that be balanced as a pregnancy approaches 39 or 40 weeks?
Answer: Prof. Smith said that 39 weeks' gestation still presents some level of risk in terms of long-term performance in education. When he talks with patients about labor induction at 39 weeks, he discusses risks such as the infant having to be in the nursery for a longer time. When counseling patients, it is important to consider individual risk factors (e.g., a body mass index greater than 45, older maternal age).

Stillbirth Prevention and Strategies

WG Recap

Robert Silver, M.D., Division of Maternal–Fetal Medicine, University of Utah Health Sciences Center

Alison Cahill, M.D., MSCI, Dell Medical School Department of Women's Health; Director, Dell Medical School Health Translation Research Institute

Dr. Silver presented on behalf of himself and Dr. Cahill, the leads for the WG. He spoke about the lack of a process in the United States for reviewing causes of stillbirths and near misses. Maternal mortality reviews might provide a mechanism for collecting information on stillbirths.

A major recommendation from the WG is to institute a U.S. stillbirth-prevention bundle, similar to those implemented in the U.K., Australia, and other countries. Dr. Silver noted that some interventions included in stillbirth prevention bundles are supported by high-quality evidence, but others are more controversial. Potential bundle elements include smoking cessation, appropriate use of low-dose aspirin, guidelines on decreased fetal movement, screening for FGR, induction of labor, patient and provider education, intrapartum hypoxia reduction, and sleep position recommendations for pregnant women. In addition, some interventions—such as universal access to prenatal and postnatal care—would have to be dealt with at the societal level, but they would affect stillbirth rates.

Dr. Silver identified research gaps in the United States and elsewhere:

- Better risk surveillance and improved risk stratification to identify pregnancies that would benefit from additional monitoring and interventions, especially induction of labor

- More intensive research of combined clinical factors, imaging, and biomarkers

- The need to mitigate disparities in stillbirth

- Tools to assess placental function

- Tools to monitor fetal movement to discern which fetuses are at risk and assess fetal growth in order to individualize risk reduction through induction of labor, if indicated

- Registries and biobanks to support research

Dr. Silver thanked international colleagues who have shared their experiences in an effort to reduce stillbirth rates in the United States.

Strategies to Prevent Stillbirth

Alexander Heazell, MBChB(Hons), Ph.D., MRCOG, Division of Developmental Biology and Medicine, University of Manchester, U.K.

Dr. Heazell referred to the _Lancet_ stillbirth series published in 2016. Absolute rates of stillbirth in 49 high-income countries in 2015 revealed a sixfold variation, with Iceland having the lowest rate at 1.3 per 1,000 live births and Ukraine having the highest rate at 8.8 per 1,000. The United States ranked 20th out of the 49 high-income countries. Of great concern is the fact that the United States had the second-lowest annual rate of reduction in stillbirth; from the turn of the century until 2015, the stillbirth rate fell by only 0.4% per year. Over the same period, the stillbirth rate in the Netherlands fell by nearly 7% per year. If all countries had achieved a stillbirth rate of 2 per 1,000 live births or less at 28 weeks' gestation, 20,000 late-term deaths could have been avoided in 2015.

Dr. Heazell pointed out that not only is there a wide range in stillbirth rates between countries; there is also significant variation within countries. The worst-performing U.S. states have rates thrice as high as those of the best-performing states. The picture is similar in the U.K., where stillbirths occur more often in some areas.

Following the publication of the _Lancet_ stillbirth series, the U.K. government announced the National Maternity Safety Ambition, which has the goal of reducing stillbirths, neonatal deaths, maternal deaths, and brain injuries that occur during or soon after birth

by 50% by 2025. Dr. Heazell said that the importance of government buy-in cannot be understated. Having an explicit government target is very important.

Thinking about how to improve care and prevent stillbirth is complicated. Dr. Heazell presented a conceptual model that begins by collecting information from a variety of sources to understand the reasons behind stillbirth. The next step is the development of interventions followed by implementation to see whether the interventions reduce stillbirths. The model includes a virtual cycle to support continual improvement.

Often underappreciated but of great importance is the perinatal audit to understand conditions linked with stillbirth and to assess perinatal care. Evidence shows that perinatal audits reduce mortality. The audit results are supplemented with confidential inquiries to ensure that care is optimal. Dr. Heazell said that evidence of suboptimal care is found in about a quarter of stillbirth cases. This information enables the development of prevention strategies.

A plethora of epidemiologic studies have identified relevant associations between various factors and reductions in stillbirth. Dr. Heazell cautioned that most risk factors have a weak to moderate association with stillbirth; targeting a single risk factor is unlikely to produce a significant reduction in stillbirth. However, one observational study in Iowa showed small reductions in stillbirths attributable solely to a maternal awareness program on fetal movement. Such reductions were not seen in neighboring states, where no comparable program existed. However, even targeting smoking alone would not allow countries to achieve stillbirth reduction targets. The odds ratio for cigarette smoking is about 1.8; currently, 8% to 10% of the pregnant population smokes. Eliminating smoking during pregnancy would make a difference, but it would not achieve the 50% reduction targeted by the U.K. government.

According to Dr. Heazell, convincing evidence is needed to ensure that an intervention produces meaningful changes. To detect a 10% drop in stillbirth from the U.K.'s baseline rate of 4% would require 371,000 participants in each arm of a trial. However, it is feasible to consider nonrandomized studies and observational data when considering the effects and unintended consequences of interventions. Modeling can give an idea of cost effectiveness as well.

The Saving Babies' Lives Care Bundle was launched by the U.K. National Health Service in April 2015 with the aim of reducing stillbirth rates. The 2023 version of the Care Bundle brings together six key elements of care:

(1) Reduced smoking in pregnancy

(2) Risk assessment and surveillance for FGR

(3) Increased awareness of reduced fetal movements

(4) Effective fetal monitoring during labor

(5) Reduction of preterm birth

(6) Management of preexisting diabetes in pregnancy

Dr. Heazell's team analyzed the impact of the Care Bundle using electronic data on 467,661 live births and 1,903 stillbirths, plus clinical audits of 720 term live singleton births and 340 pregnancies with reduced fetal movement. Stillbirths fell by 20% between 2013 and 2017. Availability of tertiary care and maternal smoking cessation interventions were significant factors in lowering rates of stillbirth. However, the same period saw increases in preterm births, elective cesarean births, and labor inductions. The cost was £160,000 per stillbirth averted. Stillbirth rates ticked up in 2021 after sustained reduction, likely from the effects of the COVID-19 pandemic. However, the term stillbirth rate held steady, and neonatal admissions for asphyxia and FGR were down.

Dr. Heazell concluded by saying that there is no silver bullet to reduce stillbirths. Medical and technical solutions do not provide complete resolution. However, because the United States has a large population and a substantial body of publicly available data, it is poised to carry out meaningful real-time studies to assess effects of interventions on stillbirth rates.

Prevention of Stillbirth: Role of Audits

Jan Jaap Erwich, M.D., Ph.D., University of Groningen, Netherlands

Prof. Erwich explained that for the Netherlands, the effort to focus intensely on stillbirth began with the 2004 European Perinatal Health Report, which showed that the Netherlands had one of the higher stillbirth rates among high-income countries. The country's shock motivated the government to form a committee, which released a report in December 2009. Although subsequent reports have shown declines in stillbirth rates, other countries have experienced larger reductions. Preterm stillbirths have not declined, however. The question is, "How can care be improved to prevent perinatal mortality and help parents who have experienced stillbirth?"

Prof. Erwich pointed out that several conditions, risk factors, or combinations thereof are relevant or lead to asphyxia and death. These include congenital malformations, FGR, preeclampsia, placental abruption, hypoxia during labor, preterm birth, and infection. Substandard care also plays a role in 10% to 20% of stillbirths.

In recent years, the Netherlands has reduced stillbirth rates by 6.8% (though other countries have achieved even greater reductions). How did the Netherlands achieve this decline? Prof. Erwich said that he does not know the answer, but most likely, a combination of factors changed during the period of decline: cooperation between primary-care midwives and obstetricians in hospitals improved; faster referral and action protocols were put into place for obstetric emergencies; thanks to new guidelines, awareness of the significance of decreased fetal movements increased among midwives and gynecologists; better education on fetal monitoring was put in place; uptake of prenatal screening increased; and programs to reduce multiple gestations contributed to the reduction as well.

Prof. Erwich also credited structured perinatal maternal morbidity and mortality audits—across all 70 obstetric units in the Netherlands—with contributing to the reduction in stillbirth rates. The Foundation Perinatal Audit in the Netherlands (PAN) was a joint effort of the government and professional colleges of pathologists, midwives, general practitioners, pediatricians, and gynecologists. The focus of PAN was initially on perinatal mortality initially, then shifted to peripartum asphyxia, followed by late preterm stillbirth.

It is important to learn from analyses of substandard care. Ways to do this include seeking answers to questions about how care could or should have been different; whether care deviated from protocols, guidelines, or "normal" care; and whether medical errors occurred. Talking about medical errors is difficult and, in some places, forbidden because of the fear of litigation. But it is necessary to have environments where health care providers can admit errors and identify solutions. Such reviews must occur in a respectful, friendly, open-minded, and nonthreatening way. An independent, respected, trained chairperson is essential because doctors are not accustomed to this sort of discussion. It took 3 years to train groups of reviewers—physicians, midwives, pathologists, and sometimes anesthesiologists and ambulance personnel.

Prof. Erwich noted that the first couple of years of audits led to the identification of thousands of substandard factors along with definitions of improvements. However, 2 years later, only a minority of improvements had been implemented properly. Nevertheless, suggestions for improving care need to be implemented to maintain the positive quality cycle. Consequently, another program started to help health providers

learn to implement suggestions, which should be framed as SMART (specific, measurable, realistic, and time-bound) goals.

Challenges to the audit process—such as fitting time into clinical schedules for a time-consuming audit—are mainly organizational. In training, reviewers learn how to review notes with "audit glasses" for conducting a root cause analysis. Everyone is motivated to improve. Any tool should be simple, and evaluation, feedback, and refinements are key to success.

In recent years, there has been a greater effort to involve parents, which is important. Patients are valuable sources of information that is usually not in medical records, such as vital information about the quality of care.

Prof. Erwich agreed with Dr. Heazell about the need for programs to address several risk factors. Specifically, meaningful reductions in stillbirth rates could be achieved through maternal smoking cessation, improved care, and hypertension treatment. Public health approaches can address health disparities stemming from social disadvantage and lower socioeconomic status. Therefore, government actions are needed.

Prof. Erwich emphasized the importance of risk management for each individual to reduce risk factors, provide optimal antenatal care, and assess fetal growth.

In Utero Program

Sarah Stock, M.D., Ph.D., In Utero, Wellcome Leap; University of Edinburgh

Dr. Stock said that Wellcome Leap is a global advanced research project for health, which, like the U.S. Advanced Research Projects Agency for Health program, follows the Defense Advanced Research Projects Agency model. Temporary project teams come together to address a program goal and achieve breakthroughs in a speedy, mission-driven way to solve important health problems such as stillbirth.

Misconceptions about stillbirth are still widespread. For example, many people believe that stillbirths cannot be prevented, and that some natural attrition is inevitable. However, Dr. Stock pointed out that at 28 weeks' gestation, many infants would be able to survive outside of the womb. Only about 7% of fetuses stillborn at up to 28 weeks have a genetic or structural abnormality. These data suggest that an improved understanding of fetal development would help determine when delivery could occur with minimal risk. The problem is that the current suite of tools is not fit for purpose. Clinical practice is based on a blood pressure cuff, urine dipstick, and tape measure (or ultrasound), and has remained largely unchanged in the last century.

The goal of the In Utero program is to find ways to model gestation such that it would be possible to halve the stillbirth rate without increasing unnecessary provider-initiated birth. Even small changes in gestational age at birth can have profound effects on child development. Critical needs to achieve this goal include the following:

- New models for predicting gestational development based on different measures

- New approaches to data collection at scale

- Scalable ways of screening, prevention, and intervention

- New technologies, measures, and biomarkers, because current tools lack the necessary resolution and cannot be used with appropriate frequency

Oxygen is fundamental to fetal survival. For oxygen to get to the fetus, there needs to be sufficient environmental oxygen for the mother to breathe, along with efficient transfer of that oxygen to the maternal circulation and then across the placenta to the fetal circulation through unimpeded flow of oxygenated blood through the umbilical cord. The fetal circulation needs to be able to pump the blood throughout the baby to enable growth and development.

Dr. Stock said that the In Utero program considers the mother, the placenta, and the fetus in a holistic way. This approach is designed to apply new technology such as computational modeling to gain a better understanding of the complexities within the system and identify new ways of intervening. This approach is particularly relevant when considering oxygen transfer from the maternal side, across the placenta, and to the fetus. The spiral arteries of the placenta have been the subject of intense study, but little is known about the venous return to the mother. Oxygen transfer is complex because it depends not only on the arterial supply but also on venous drainage. Dr. Stock demonstrated how to use a mathematical simulation to interrogate the effect of different venous configurations in the placenta. The simulation emulates the maternal flow during one cardiac cycle and reveals variations in the oxygen concentration that depend on the number or configuration of veins draining. This suggests that oxygen transfer depends on the venous drainage as well as the spiral arteries.

The In Utero researchers discovered the idea of placental contractions, which occur apart from uterine contractions and flush out blood; this allows fresh, oxygenated blood into the placenta to enhance transfer to the fetal circulation. Magnetic resonance scans can be used to study the frequency of this phenomenon and understand its significance in placental oxygenation on the maternal side.

Dr. Stock explained that on the fetal side, images of the placenta created with the European Synchrotron revealed the great complexity of the villi. The team is taking these complex images, segmenting and skeletonizing them, and using them in models of placental oxygen transport at different scales.[2] The new computational models provide unique ways to assess maternal vasculature, vascular response, and hemodynamics. Advanced imaging techniques are directly examining placental function and flow. Now the team is looking at wearables, including wearable ultrasound and monitors to investigate continuous blood flow and fetal movement.

Further studies are relying on cancer technologies to detect rare placental cells in the maternal circulation. One trophoblast cell might be found among 10 million white cells. A team in Seattle, Washington, is isolating these cells and sequencing them—essentially a noninvasive biopsy of the placenta. A team in London is developing a wearable monitor that can track placental oxygenation.

In total, 17 teams are working on different aspects of the problem. Dr. Stock said that the program, which has been underway for 16 months, represents a $50 million investment.

Addressing Stillbirth in Australia: Video Remarks

Vicki Flenady, Ph.D., M.Med.Sc., National Health and Medicine Research Council Centre for Research Excellence in Stillbirth, Brisbane, Australia

Prof. Flenady described dramatic progress in reducing stillbirths in Australia since 2016 by collaborating with politicians, parents, and stakeholders to create the National Action Plan, which was signed by all the country's public health units. Implementing best practices are being disseminated through Australia's Safer Baby Bundle. Australia will implement a new guideline across hospitals shortly.

The Australian Safer Baby Bundle is a national initiative focused on improving five elements to reduce stillbirths: (1) smoking cessation, (2) identification of women who are at increased risk of fetal growth restriction, (3) detection of decreased fetal movements, (4) safer sleeping (on side), and (5) shared decision making to reduce the risk of stillbirth through proper timing of delivery. The goal is to reduce stillbirth from 28 weeks to term by 25% by 2025.

---

[2] Clark, A. R., Chernyavsky, I. L., & Jensen, O. E. (2023). The complexities of the human placenta. *Physics Today, 76*(4), 26. https://doi.org/10.1063/PT.3.5216.

As Prof. Flenady explained, the Australian Safer Baby Bundle was modeled after the U.K. bundle. The set of recommendations resulted from the collaboration of maternity services and policymakers with input from parents. The bundle has a significant suite of resources for women and clinicians, including slides and posters that have been culturally adapted for subgroups, including migrant and refugee populations.

Prof. Flenady presented a timeline showing efforts in Australia to reduce perinatal mortality. The Center for Research Excellence (CRE) in Stillbirth, established in 2016, brought together politicians, policymakers, researchers, clinicians, and parents. An Australian Senate inquiry in 2018 led to the National Action Plan, which was launched in 2020. The major priority areas in the plan include ensuring high-quality stillbirth prevention and care, ensuring holistic bereavement care and community support, prioritizing stillbirth research, raising awareness, strengthening education, and improving stillbirth data collection. The need to reduce disparity by improving culturally responsive care cuts across all the priority areas.

One key finding from the Safer Baby Bundle implementation was the importance of having timely data to monitor implementation and effectiveness. Many jurisdictions developed new systems to collect these critical data elements to inform practice and continually improve. Implementation of the bundle has been a massive effort across Australia—by individual maternity services, state and territory health departments, and the federal government, which has promoted and funded it.

Prof. Flenady reported that the Safer Baby Bundle is undergoing evaluation, and she shared some snippets:

- Clinicians report having more conversations with women about stillbirth regardless of their risk status. Women need the information and how they can reduce their risk.

- Health care professionals report that conversations about stillbirth have become more routine, and clinicians are more comfortable in their discussions with women.

- It appears that iatrogenic delivery at early-term gestation is not increasing at bundle sites, which is very encouraging.

The 2024 edition of the comprehensive guideline includes sections on perinatal palliative care, expanded sections on care during subsequent pregnancy, and a framework for care around stillbirth and neonatal death. Versions of the guidelines for

parents have also been published and adapted for Aboriginal people. Other guideline resources include information about autopsy and other investigations.

Prof. Flenady reported that an RCT of an online program titled "Living with Loss" was recently completed.

The CRE for Stillbirth's IMproving Perinatal Mortality Review and Outcomes Via Education (IMPROVE) program targets health care providers and maternity services to provide best-practice care for families in the immediate period after a perinatal death. IMPROVE convened a face-to-face workshop and launched an e-learning program. The next IMPROVE workshop will be held in Utah in 2024.

Prof. Flenady concluded her remarks by highlighting the importance of parents' voices in shaping stillbirth research and care. A guide for bereaved parents will be published soon. It suggests meaningful ways for families to be involved in stillbirth research.

Moderated Discussion

Drs. Reddy and Longo co-moderated the session.

Question: Dr. Dieke asked Dr. Heazell about procedures for confidential enquiries.
Answer: Dr. Heazell said that the committee selects cases at random, then approaches providers to request the case information. The next step is anonymization of the information. The committee then grades the care given as "Likely not to affect the outcome," "Possible effect on the outcome," or "Unlikely to affect the outcome." Typically, the committee receives a great deal of granular data, and themes emerge that allow members to focus on ways to potentially improve care.

Question: Prof. Lens asked about ways to overcome the myth of stillbirth inevitability.
Answer: Dr. Heazell said that data from around the world show that there are effective ways to reduce stillbirth rates and dispel ideas about inevitability.

Question: Prof. Lens asked about barriers to physician participation in confidential inquiries. Would there be more resistance in the United States?
Answer: Dr. Heazell said that the cases for the inquiries are completely anonymized. No one knows where they came from.

Comment: Dr. Gold runs a program in Detroit, Michigan, where many women have clusters of risk factors, but the program has few resources to address them.
Answer: Dr. Heazell said that the bundle is designed to be quite comprehensive based on the notion of accumulated risk. Patterns of stillbirth in the U.K., for example, show

clear overlaps with child poverty. Maternity services are designed to address that, but a major approach is needed to address multiple risk factors.

Question: Dr. Dudley asked about messaging to government leaders in order to get their buy-in—especially in countries where there is growing distrust in public health measures.
Answers: Prof. Erwich recommended recruiting a champion, such as a politician who has experienced a stillbirth. He offered the example of a particular African country that had a woman minister of health and was able to make great progress under her leadership. Dr. Heazell agreed on the importance of lining up champions. He also suggested pointing out that stillbirths are "not free." In fact, the economic and psychosocial costs are significant.[3] In addition, he recommended approaching politicians with specific, tractable requests—such as seeking support for confidential enquiries or care bundles—instead of just stating that stillbirth rates are too high. Dr. Longo pointed out that balance between stillbirths and costs in terms of earlier delivery and more cesarean sections.

Question: How is it possible to show the likely worth and cost of implementing some measurements included in the bundle (e.g., blood testing and ultrasound exams)?
Answers: Dr. Heazell said that it is a matter of political will and providing assurance that bundles are going to have the desired effect. Prof. Erwich suggested making a plan and identifying the pros and cons of implementing tests or a bundle. He said that an implementation that fails is worse than one that never started because of the loss of resources. Dr. Heazell emphasized the importance of learning from programs and ensuring that learning systems are in place.

---

[3] Heazell, A. E. P., Siassakos, D., Blencowe, H., Burden, C., Bhutta, Z. A., Cacciatore, J., Dang, N., Das, J., Flenady, V., Gold, K. J., Mensah, O. K., Millum, J., Nuzum, D., O'Donoghue, K., Redshaw, M., Rizvi, A., Roberts, T., Toyin Saraki, H. E., Storey, C., Wojcieszek, A. M., … Lancet Ending Preventable Stillbirths Investigator Group. (2016). Stillbirths: economic and psychosocial consequences. *Lancet (London, England), 387*(10018), 604–616. https://doi.org/10.1016/S0140-6736(15)00836-3.

Improving Data Collection

WG Recap

George Saade, M.D., Eastern Virginia Medical School

Mikyong Shin, Dr.P.H., M.P.H., RN, CDC

Dr. Shin said that the Improving Data Collection WG focused on various challenges and other considerations related to data collection on fetal death. A strong recommendation of the group was to standardize the definition of stillbirth, particularly regarding gestational age. Most entities define stillbirth as an instance in which an infant is born with no signs of life. Yet definitions vary based on gestational age, weight, length, or other criteria.

The National Center for Health Statistics' definition reads as follows: "Fetal death refers to the spontaneous intrauterine death of a fetus at any time during pregnancy. Fetal deaths later in pregnancy (at 20 weeks of gestation or more, or 28 weeks or more, for example) are also sometimes referred to as stillbirths."

Dr. Shin reported that the group also raised concerns about the ability to identify stillbirths and discussed CDC's Pregnancy Risk Assessment Monitoring System, surveys, and electronic health records (EHRs) as data sources for identifying stillbirths. Regarding the fetal death certificate, the WG recommended training for OB/GYNs and perinatal providers on best practices for reporting information on fetal death certificates. Also discussed was artificial intelligence (AI) as a means for obtaining missing information (though this approach is probably not going to be effective if the data are not already available).

The group also discussed ways to obtain patient permission for accessing records, use of software solutions for health care organizations, and the idea of developing a centralized approach to data collection, perhaps by establishing a center of excellence.

Dr. Saade reported on the group's discussion of the completeness, timeliness, and accuracy of data from stillbirth workup. Much of the discussion centered on autopsy—specifically on compensation, payment, or coverage to cover the costs, as well as the need to have qualified personnel, pathologists, or subspecialists to perform autopsies and interpret the results.

Dr. Saade pointed out that the system is not optimized for delivering results to patients or for reporting to the authorities that track stillbirths. The group suggested that stillbirth

workups could be considered a quality measure. To do so would require advocating with professional organizations and payors to add placental pathology, autopsy, and data completeness as a quality measure. Novel methods are needed to follow up with patients, including counseling at the time of bereavement or later via telehealth.

Machine Learning and Its Application in Stillbirth

Tetsuya Kawakita, M.D., M.S., Eastern Virginia Medical School

Dr. Kawakita reviewed the history of computer advances over the years and explained that "AI" is a general term for technologies that learn to perform tasks that require human intelligence. Machine learning (ML) is a type of AI that uses computer algorithms to learn and identify patterns in datasets.[4] ML can handle tabulated data and process images, sounds, or videos. Supervised learning can train the algorithm via labeled data, so having known outcomes is necessary. Unsupervised learning, such as clustering of patients based on food intake patterns, can sort unlabeled data based on shared characteristics. Reinforcement learning refers to ML that learns based on feedback—a reward or a penalty.

ML differs from conventional statistics, such as linear or logistic regression, in that statistics typically assuming that data are generated by some underlying stochastic process, which results in a normal distribution. Also, statistical approaches are based on a priori assumptions and a limited set of selected variables, introducing a potential source of investigator bias. In contrast, ML is not based on how data are generated and can handle many variables. AI and ML are sometimes criticized because of their "black-box nature," which makes understanding how predictions came about difficult.

AI and ML applications in medicine that are better accepted include reading of electrocardiograms, white cell differential counts, and analysis of photographs of the retina and cutaneous lesions. AI and ML can also help with clinical trials by identifying eligible individuals and supporting recruitment and retention efforts.[5]

Dr. Kawakita said that ML can handle predictions at the individual or population level. He provided an example of using ML for estimating treatment effects and said that this

---

[4] Haug, C. J., & Drazen, J. M. (2023). Artificial intelligence and machine learning in clinical medicine, 2023. *New England Journal of Medicine, 388*(13), 1201–1208. https://doi.org/10.1056/NEJMra2302038.
[5] Zame, W. R., Bica, I., Shen, C., Curth, A., Lee, H. S., Bailey, S., Weatherall, J., Wright, D., Bretz, F., & van der Schaar, M. (2020). Machine learning for clinical trials in the era of COVID-19. *Statistics in Biopharmaceutical Research, 12*(4), 506–517. https://doi.org/10.1080/19466315.2020.1797867.

approach could be helpful in the setting of RCTs for identifying people who might be eligible, or for identifying patients who benefited from a therapy.

Dr. Kawakita highlighted several ML applications in obstetrics and gynecology:

- Prediction of maternal readmission within 6 weeks postpartum

- Prediction of success with vaginal birth after cesarean delivery

- Prediction of postpartum hemorrhage

- Prediction of stillbirth based on data available before 24 weeks' gestation[6]

Regarding the study on stillbirth, Dr. Kawakita said that it was a secondary analysis of data collected by the Stillbirth Collaborative Research Network Study on 3,000 live births and 982 stillbirths. The analysis considered 101 variables. Despite the algorithm's black-box nature, it identified important variables including previous stillbirth, gestational age at the earliest prenatal visit, and second-trimester serum screening.

Dr. Kawakita highlighted potential future applications of AI in medicine, including data collection via neural language models, support of clinical encounters as personal scribes, prompting of clinicians to ask key questions for differential diagnosis, and answering patients' questions.[7] ML could also help reduce risk of stillbirth by using clinical information, demographics, and ultrasound information, then recommending increased antenatal testing. Future work could focus on reducing bias in AI and ML, incorporating human values into algorithms, and weighing issues related to answering questions relevant to regulators.

Dr. Kawakita pointed out some limitations of ML, including the need for a large sample size. But no standard way to estimate required sample sizes exists. For imaging studies, the rule of thumb is to include at least 1,000 patients. Yet many studies enroll only a few hundred patients. That means that models lack computational power. In

---

[6] Cersonsky, T. E. K., Ayala, N. K., Pinar, H., Dudley, D. J., Saade, G. R., Silver, R. M., & Lewkowitz, A. K. (2023). Identifying risk of stillbirth using machine learning. *American Journal of Obstetrics and Gynecology, 229*(3), 327.e1–327.e16. https://doi.org/10.1016/j.ajog.2023.06.017.

[7] Sahni, N. R., & Carrus, B. (2023). Artificial intelligence in U.S. health care delivery. *New England Journal of Medicine, 389*(4), 348–358. https://doi.org/10.1056/NEJMra2204673.

addition, ML takes time and is costly due to the reliance on cloud computing and computers.

Regarding the black-box nature of ML, Dr. Kawakita said that using the Shapley Additive exPlanations framework could help improve visibility into how ML models work. AI and ML also raise some ethical challenges, such as the risk of increasing unemployment if less human labor is needed. In addition, there are privacy concerns about collecting and using personal data, especially health care information, in algorithms.

In conclusion, Dr. Kawakita said that use of AI and ML is expanding and could support research and clinical care to help reduce stillbirths.

Data-Driven Strategies to Augment Maternal Health Delivery

Vesela P. Kovacheva, M.D., Ph.D., Harvard Medical School

Dr. Kovacheva's presentation focused on data sources that could support ML use in clinical practice, barriers to data access, and examples of implementation of data-driven strategies for predicting stillbirth risk or supporting decision making in stillbirth.

Big Data is part of daily clinical practice. As an anesthesiologist, Dr. Kovacheva uses a great deal of data, including structured data from EHRs and unstructured data from clinical notes. Imaging—including obstetrical ultrasound and point-of-care ultrasound—is becoming more important. An increasing number of patients are genotyped as well. It is estimated that for each patient, a billion data points are generated each day. This enormous wealth of information presents a tremendous opportunity for analysis and improved care.

Dr. Kovacheva envisions an ideal scenario that uses ML as a predictive tool for assessing risk for rare adverse maternal outcomes (i.e., stillbirth) in a large patient population consisting mainly of low-risk patients. With a diverse population and well-curated data, it would be possible to develop a high-performing ML model and use it to generate predictions. The output could be used to triage high-risk patients, allocate resources (e.g., ensure that staff on hand), and provide early diagnosis and personalized care.

Why are such tools not part of clinical practice today? Dr. Kovacheva explained that one of the main reasons is lack of data access. It might take a month or more to obtain a dataset from EHRs. Access is heavily regulated to respect patient privacy, and many institutions have outdated infrastructure. Some tools are so outdated that they are no

longer supported by developers, which requires new code to adapt modern tools to work with a database. In addition, medical records need extensive cleaning to avoid introducing noise into datasets.

To overcome such limitations and support collaboration between clinicians and data scientists, Dr. Kovacheva set up a lab that uses the latest tools for ML data science, population genetics, and statistics to improve maternal health. The tools developed in the lab first aimed to overcome barriers with data access and data cleaning. The scientists developed the Medical Record Longitudinal Information AI System (MERLIN) platform, which can accommodate diverse health care data and provide security and patient confidentiality. The system, which can handle multiple projects in parallel, is optimized for ML.

Dr. Kovacheva explained how MERLIN works in real time. The scientists generated a dataset of 100,000 entries for 80,000 synthetic patients, then kept increasing the number of variables in the datasets. The datasets could be generated in just a few minutes and support multiple ML projects.

One of the first conditions the scientists explored was a predictive model for preeclampsia (XGBoost model) using a combination of clinical and genetic data available through a biobank linked to EHRs. Data from 121 pregnancies were used to develop models for two points: (1) early pregnancy and (2) late pregnancy. The best-performing model was the ML model using only clinical data; adding genetic data did not improve predictions. The early-pregnancy model could be used to identify patients at risk who might benefit from early prophylaxis, such as home blood pressure monitoring. The same approach could be used to predict stillbirth as well. For the late-pregnancy model, genetic risk scores did not improve risk predictions either. Dr. Kovacheva speculated that this type of model could be used to optimize care when several patients are admitted at once; this would help the physician decide whom to examine first, and even notify the neonatal intensive care unit to save a bed.

Dr. Kovacheva concluded by encouraging greater use of the diverse and extensive data available in clinical practice. Limitations can be overcome, she said, and exciting new opportunities are on the horizon.

Improving Data Collection Through AI

Noémie Elhadad, Ph.D., Columbia University

Dr. Elhadad identified two data types that would be useful in stillbirth research: (1) data from EHRs and (2) data from self-tracking apps and wearable devices. AI approaches

could be leveraged to extract actionable insights and learn how to predict events better and faster.

Self-tracking data and wearables offer many advantages. For one thing, they provide a picture of the patient experience and are longitudinal in nature. There has been strong engagement by women with mobile health apps, and when the devices are well designed, they can meet informational needs of individuals. Well-designed apps are also able to capture data from very diverse populations.

Nevertheless, challenges exist, including data quality and accuracy, missing data (especially with active data collection), and the lack of calibration from one individual to the next. There is much work ongoing with ML to overcome such issues.

Dr. Elhadad explained that challenges with data integration and standardization are a common theme across all data in health and health care. There have been many advances with mobile health, but different types of devices can introduce variation in data. Also, wearing a device can also lead to behavior changes. It is important to think of value-based and inclusive design to reduce bias and ensure representativeness of the data collected. In summary, self-tracking data adds valuable context that reflects patients' experience.

The advantages and challenges of EHR data are well documented. Dr. Elhadad said that valuable longitudinal data can be leveraged for research and clinical decision-making, and the data collection is not hypothesis driven. One challenge is heterogeneity of data, which come from clinical notes, structured data, and images, but there can be random and nonrandom data missingness. Much work with ML in health care is focusing on overcoming these challenges. Also, when considering ML approaches to handling EHR, one must be mindful about potential bias, because some doctors might order certain tests that others do not.

Interoperability and standardization are major challenges. Many solutions are based on centralization and federated structures whereby different institutions are agreeing on standard data collection and common data elements.

Dr. Elhadad pointed out that with EHR data processing, a major question is how to distinguish institutional practices from population and individual patient characteristics. Those two things are highly conflated in EHR data. Because much information is in the form of clinical notes, capabilities such as natural language processing (NLP) are going to be critical.

Dr. Elhadad said that the goal for AI or ML is to predict events earlier than humans currently can, so that there is a larger window of opportunity for intervention. She described four types of AI or ML tasks:

(1) Descriptive ML uses large amounts of data to identify patterns and trends in a supervised or unsupervised way.

(2) Predictive modeling is probably the most public facing of ML and AI applications. It aims to forecast future outcomes and provide a basis for risk estimation. An example is a study using predictive AI to assess risk of deterioration of patients in intensive-care units.

(3) Prescriptive ML can suggest actions for achieving a goal. For example, based on current information and information from 12 hours ago, prescriptive ML could potentially formulate a plan for weaning a patient off a ventilator.

(4) Generative ML uses a large amount of data at a local level to generate original content. These models do not incorporate causality or mechanistic modeling. ChatGPT is an example.

NLP can be generative or extractive. It might be useful for tasks such as generating discharge summaries, which is not easy even for humans, yet NLP can now achieve human level or better when it comes to synthesizing information. Extractive NLP extracts important information to standardize patient characteristics, such as social determinants of health.

Dr. Elhadad presented an example of how ML could help answer the question of who might benefit from an intervention for chronic kidney disease. A predictive model based on survival data might be able to identify themes in discussions and clinical notes. Another example related to phenotyping endometriosis. The big question in leveraging patient data is identifying what one wants to extract from patient records. Focus groups and online forums can help identify types of data that would be useful. EHRs only contain information from clinical encounters, but it is also important to collect information between visits.

Moderated Discussion

Drs. Barfield and Longo co-moderated the session.

Question: Dr. Barfield thanked the presenters who delivered informative remarks on AI, ML, and novel data collection methods. These approaches can yield rich collections of

data, but what about gathering information from patients who are often not seen or heard because of visitation barriers or issues related to systematic bias? A rich array of information is not being collected to develop AI models or be analyzed by AI.

Answers: Dr. Elhadad said that data missingness is a problem. For example, clinical notes may have poor documentation for some groups. Data need to be aggregated from a variety of sources, including wearable devices, to get a fuller picture. For patients who are not seen by the health system, the *All of Us* Research Program might be a source of valuable data because it has been able to enroll many people from populations that have historically been underrepresented in biomedical research. Dr. Kovacheva recommended patient advocates as potential sources of information and support. For example, doulas can speak to patients in their own language and bring them into health care. She also said that her team conducted a survey of patients to explore their perspectives on use of AI in health care. People were generally open to the idea, but there is a need for more resources to help them understand the technology. Dr. Kawakita spoke about the need to collect data from women who go to emergency rooms during their pregnancies but do not attend office visits. One possibility is to work with patient communities and patient advocates to try to engage those women.

Question: Dr. Barfield asked whether and how AI can integrate physiologic pathways, and what challenges that would entail.

Answers: Dr. Kawakita said he thought that integrating physiology was an interesting idea. Dr. Elhadad said that there is much interest in integrating physiologic models, hormone dynamics, and glucose levels into predictions; inclusion of mechanistic pathways is the future of AI. Dr. Kovacheva referred to Prof. Smith's presentation and noted that integrating metabolomics data and biomedical knowledge in ML models would improve the accuracy of predictions.

Question: Dr. Saade posed a question that applies across obstetrics. Many outcomes are not defined as well as they are in cancer, for example. In obstetrics, there is imprecision, noise, and some subjectivity in terms of outcomes. This means that there is no "natural course of disease" for comparison to interventions. How does one adjust for this in AI or ML models?

Answers: Dr. Elhadad agreed about the challenges in understanding outcomes. In models, phenotype definition fields can help identify proxies that allow discernment of particular outcomes for patients. This approach depends on what is in EHRs. Regarding the lack of a "natural course of disease," Dr. Elhadad said that that is where complementary sources of information from before and during pregnancy outside of clinical encounters could help. Dr. Kawakita pointed out the need to calibrate ML models so they could work in a variety of settings.

Question: Dr. Wojcik asked whether fetal polygenic risk scores come from fetal models or are strictly based on the maternal side.
Answer: Dr. Kovacheva spoke about the lack of good datasets. Maternal and fetal genetics is very challenging. Polygenic scores are largely based on populations with European ancestry, so their applicability to more diverse populations is limited. There is a need to prospectively collect more data on genetic risk from many individuals to really enhance the understanding of disease in the mother and the baby.

Question: Dr. Wapner observed that obstetrical care is highly siloed, so relevant information is stored in a variety of records (e.g., inpatient, outpatient, genetic testing, the infant's). Is there a way to aggregate all these data to apply AI approaches?
Answer: Dr. Barfield responded that linking data, especially from the mother's pregnancy and her infant, is an ongoing effort. These data need to be more readily available to clinicians.

Dr. Longo presented some questions that members of the public submitted:

Question: What is the role of the placenta? How can its contribution to maternal-fetal health be captured in predictive AI and ML models?
Answers: Dr. Kovacheva said that models can incorporate information from clinical notes, ultrasound reports, and imaging that would reflect placental health. Modelers could then add or subtract different types of information from a model to assess the effect on the model's predictive power. Dr. Elhadad said that it is important to consider whether the vision is to use AI at the point of care or just in research. The intended use would affect the collection of data.

Question: To help with assessment after a stillbirth, it is important to update the medical record to ensure that data collected later are incorporated. How can challenges in obtaining vital records (e.g., birth or death certificates) be overcome?
Answer: Dr. Barfield agreed that autopsy information needs to go back to the families, but that takes time. It also takes time and effort to revise vital records. Sometimes it takes months to get results. With regard to vital information reporting, she said that some variables have been poorly reported, but now more data on stillbirths is being included in some states.

Enhancing Resources for Families Affected by Stillbirth

WG Recap

Jill Wieber Lens, J.D., University of Arkansas School of Law

Karen Gibbins, M.D., MSCI, Oregon Health & Science University

Dr. Gibbins said that the group's focus on enhancing resources for families ended up overlapping with prevention. The tragedy of stillbirth is what happens when prevention fails. How can providers care for the family and affect lifelong outcomes?

There are well-documented inequities in outcomes and in care. The WG emphasized the importance of the United States providing a continuum of care when families experience stillbirth, including information and counseling when stillbirth is diagnosed, the provision of memory-making opportunities, postpartum follow-up, mental health care, and community and peer resources.

Dr. Gibbins also emphasized the importance of training for staff, perhaps based on the Alliance for Innovation on Maternal Health bundle that provides training on standards and on trauma-informed care. To this end, the WG recommended assessing currently available educational options and strategizing ways to incorporate training to support grieving families.

Advocacy and policy goals should encompass assessments of the economic burden of stillbirth, including costs of workup and funeral expenses. It would be important to ensure widespread access to autopsy and genetic testing and counseling.

Dr. Gibbins said that many families are shocked that stillbirth still occurs in the United States in the 21st century. The WG recommended providing education on stillbirth during prenatal care, along with information on reducing risk and enhancing awareness of the importance of monitoring fetal movement.

The WG advocated more research on mental health care, including screening and intervention. There is little research on patient experience or needs with regard to bereavement care. The information that does exist has little representation from marginalized groups. More research is needed on patient experience.

Hearing Our Stories: Exploring Provider Empathy for Families Experiencing Stillbirth

Nicole Alston, M.S.W., Columbia University

Ms. Alston experienced the loss of Skye, a daughter who was stillborn because of placental abruption. She said that there is no preparation for parents who experience this macabre reality. She is committed to doing as much as possible to end the horrible experience of stillbirth. Ms. Alston shared a poem she wrote titled "I Wish," which was set to an animation and posted on OK2Grieve, an online forum that she founded.

Many individuals have a lifelong goal of motherhood and take joy in their pregnancy. When Ms. Alston arrived at the hospital, the painful reality of despair, intense sadness, isolation, and loneliness contrasted with her expectations. Skye's death was never contemplated, so there was no preparation. Now, as time goes on, the gap continues as Ms. Alston had expected to watch Skye grow up and achieve milestones.

In her role as a community liaison and practicum instructor at the Center for Prolonged Grief at Columbia University, Ms. Alston has heard stories from parents who have also experienced stillbirth. She shared a few (with the families' permission):

- Mom YA had two stillborn babies. Years later, she still has trouble sleeping—a horrible reminder of her loss.

- Mom DW said she lost a major part of herself and who she thought she would become. She had a traumatic experience in the hospital when she was mistreated by hospital staff. After enduring intense labor, the silence was absolute. There was no baby's cry. The medical providers left the room, and Mom DW's grandmother was the only one left to tell her about the stillbirth. She said she still buys a cake every year to commemorate her son's birthday.

- Mom DM gave birth to a stillborn baby at 25 weeks. The father had asked to cut the cord, but the provider did it instead—thus depriving the father of a special and final opportunity to care for his child.

- Dad PA is the father of Baby S, stillborn at 40 weeks. Dad PA said, "Down in my gut, there's such an empty feeling, and I don't know if that void can ever be filled." The baby had responded to his voice while *in utero.*

Ms. Alston also provided the perspective of CM, who was her labor and delivery nurse: "Every anticipation of a joy is stolen from the mother when we tell her that we're sorry, but there's no heartbeat."

Ms. Alston said that every family has the right to grieve in the way they wish. She emphasized the importance of providing families with needed support.

Improving Surveillance for the Hidden Half of Fetal-Infant Mortality

Lauren Christiansen-Lindquist, Ph.D., M.P.H., Emory University

Dr. Christiansen-Lindquist said that good data must be put into algorithms so that models provide good outputs. Stillbirth reporting in the United States is wrapped up in vital statistics registration—fetal deaths are considered vital events—which is a decentralized process.

Fetal death refers to the spontaneous intrauterine death of a fetus at any time during pregnancy. Reporting varies somewhat from state to state, but most require reporting at 20 weeks' gestation or a birthweight of 350 grams. Some states require reporting at 28 weeks' gestation. Dr. Christiansen-Lindquist said that data on stillbirths that occur at 20 to 27 weeks' gestation are not complete.

Some data come from the facility where the stillbirth or fetal death was reported or occurred, and some data (demographic) come from the patient. Fetal death certificates are much more likely to have missing data compared with stillbirth death certificates. Dr. Christiansen-Lindquist demonstrated misreported and missing values in data from two U.S. cities. Across the 57 reporting areas in the United States, the cause of fetal death is missing in 13.4% to 93.5% of reports. In 2021, 36.8% used the International Classification of Diseases, 10th edition, code for fetal death of unspecified cause. When the fetal death certificate was filed, only 19.3% had or planned to have an autopsy conducted. Timeliness of reporting has improved, but the lag is much longer for reporting fetal deaths than live births.

Substantial efforts have been quite successful in improving birth certificate data. With focused effort, similar improvements could be made with fetal death data. Expanding the Pregnancy Risk Assessment Monitoring System (PRAMS) database to include stillbirth data is an opportunity.

Dr. Christiansen-Lindquist reported on progress achieved through the Study of Associated Risks of Stillbirth (SOARS), a mailed questionnaire with telephone follow-up that has been implemented in Utah and North Dakota. SOARS data are helpful in

identifying and offering resources to families. For example, findings from SOARS show that families were offered opportunities to have mementos created, but seldom to wash and dress their infants.

More states would benefit from participation in SOARS, but some would first need to improve vital statistics reporting to take part. The data can be used to improve care for mothers and families who experience loss.

Supporting Bereaved Parents Experiencing Pregnancy and Infant Loss

Kathleen Massmann, M.S., Healing Moments Counseling

Ms. Massmann said that for her, grief is the process by which people miss that which has been lost. It is normal, natural, and expected. Perinatal loss, however, is both poorly understood and isolating.

Ms. Massmann presented a timeline of research on grief. Historically, stillbirth was often met with silence. Mothers were often immediately separated from their babies and other mothers. Medical professionals were less likely to remember circumstances of stillbirths. Research now shows that parents who engage in memory-making experiences often adapted better, and acts such as bathing and touching their stillborn infants had positive impacts on depression and mood disorders. Parents who have a chance to hold their babies have an easier time reconciling their expectations with the loss. However, because of cultural and gender differences, being careful with assumptions about how parents grieve is important.

Current research shows that stillbirth can lead to guilt, shame, and even posttraumatic stress disorder (PTSD) symptoms. Stillbirth mothers often report feeling that something was wrong with their pregnancies.

Ms. Massmann urged caution in diagnosing major depressive disorder in grieving parents. Such a diagnosis may be stigmatizing. By definition, major depressive disorder must last at least 2 weeks, and prolonged grief disorder is characterized by a loss that occurred at least a year prior. Parents need understanding, not a diagnosis. Jennifer Westby has a process by which grieving people heal. Feelings come in waves of varying intensity. Memorializing, meaning-making, and the passage of time all contribute to grief resolution.

Ms. Massmann said that group or peer-to-peer support in hospitals and at home can help families. However, differences in grieving exist and must be acknowledged. Too

often, grandparents are ignored, but they are experiencing a dual loss: their grandchild and the person that their child was before the stillbirth.

Ms. Massmann identified three main areas to focus on: (1) providing compassionate care, (2) being a companion in grief, and (3) making appropriate referrals. She recommended mirroring parents' language by using the child's name or referring to their baby. She also advocated pausing before prescribing medication after a loss. Positive intent of providers should be assumed; prescribing may be an action they take in an effort to help. Nevertheless, providers need to be careful to avoid adding to trauma.

From their moment of loss, parents are compiling a new story, and providers are part of that story. Ms. Massmann recommended offering information and choices to parents while being mindful of their own triggers in order to avoid adding to parents' trauma. Providers may make mistakes, but people will feel their good intentions. Parents should be offered every chance to make memories and interact with their babies.

Ms. Massmann concluded by revealing that she is a three-time bereaved parent. Parents are forever changed by pregnancy loss or infant loss.

Moderated Discussion

Prof. Lens and Dr. Longo moderated the session. They thanked the presenters for sharing their deeply personal stories.

Question: Dr. Dieke asked about the type of workforce that is most helpful for parents in terms of offering grief support and help with the transition to their new reality.
Answer: Dr. Massmann said that the best professionals are counselors for providing support after stillbirth, but few professionals are well trained in grief counseling. Poorly done grief work runs the risk of adding trauma on top of trauma.

Question: Prof. Lens asked how mistreatment by professionals affects parents who are grieving.
Answers: Ms. Alston said that mistreatment can prevent or delay parents from getting their lives on track, especially in communities that question the acceptability of grieving. Mistreatment during grief can also affect parents' connections with future children, increase the risk of long-term resentment, and give them a sense that their loss was deserved. Ms. Massmann said that on one hand, mistreatment can affect parents' trajectories for a lifetime; on the other hand, counselors and medical professionals who respect parents' wishes, use the infant's name, and offer to bathe, touch, or dress the infant can be sources of great comfort who help ease parents' grief.

Question: Dr. Gibbins asked how to frame trauma as a response to stillbirth. Is the concern about PTSD?
Answers: Ms. Massmann suggested screening parents of stillborn children for PTSD, though the trauma they may experience is not necessarily PTSD per se. Ms. Alston added that everyone's story is different. One time, she said, she went to a mother's bedside, but the mother indicated that she had come to terms with the loss and was OK.

Question: Prof. Lens asked about the possibility of expanding SOARS to other states.
Answers: Dr. Christiansen-Lindquist said that CDC issued another opportunity for states to apply for additional funds to add onto PRAMS, but there have not been many applications. The reasons for the low response rate are unclear, but learning more and addressing any barriers that exist would be worthwhile. Dr. Dieke noted an opportunity through the CDC Foundation to collect maternal self-reported stillbirth experiences in other jurisdictions.

Question: Guillermina Girardi, Ph.D., M.Sc., asked how providers can help parents avoid or overcome feelings of self-blame and guilt. Would having more information from fetal autopsies help?
Answer: Ms. Alston said that a one-size-fits-all approach will not work, because each situation is different. Some parents find it helpful to hear someone say that the stillbirth is not their fault, and sometimes a message can be communicated just through group presence. Bedside staff should say that they are available to answer questions, and of course be prepared to do so. Ms. Massmann cautioned, however, that some mothers cannot be dissuaded from the belief that the stillbirth is their fault. She suggested "imaginative conversations" in these instances, to reinforce that the mother did everything she could to protect her baby and remind her of the love and care she poured into that pregnancy and birth. Dr. Parast recalled speaking to a patient and sharing that the placenta showed chorioamnionitis. The patient was relieved to hear that the cause of stillbirth was something in the placenta that she could not control. Simple information can be very helpful. Dr. Gold said that the issue of guilt is important. It is often not a rational reaction, so just presenting the facts may not address the underlying beliefs.

Question: Dr. Dieke asked what happens when families go home.
Answers: Ms. Alston said that when parents come home to an empty crib, there is no way to fill that void. Parents lament the lost opportunities for joy, positive memories, and achievement of developmental milestones. They feel lonely and disconnected. Ms. Massmann said that often the hardest time may occur later, after the sympathetic phone calls, visits, and cards stop coming. She added that the highly publicized one-year time frame of grief is artificial and not grounded in reality.

Comment: Dr. Cahill mentioned family pressures or expectations, and she suggested that more comprehensive educational opportunities for family members could be helpful, especially for multigenerational households.

Dr. Longo and Prof. Lens presented questions submitted by members of the public:

Question: What are the main obstacles to providing grief support?
Answers: Ms. Massmann said that each situation is different. Important barriers include having few providers who have grief training, lack of insurance coverage, and lack of other funding for grief support services. Dr. Dieke said that data from Utah suggest that people sometimes do not know where to access grief resources.

Question: How do you see being able to implement training to help providers understand and better cope with the tragedy of stillbirth?
Answer: Ms. Massmann spoke about the need for more educational opportunities, perhaps coupled with requirements for licensure to participate in such trainings. It will have to begin with a desire for change in order to help stillbirth support become common knowledge for therapists.

Reactions to WGs' Presentations

The co-leads of the WGs responded to the foregoing presentations and discussions.

Stillbirth Prevention and Strategies

Dr. Silver said that stillbirth is not just a medical problem. The United States must learn from experiences in other countries, and international collaborations provide a way forward.

Dr. Silver also observed some areas of overlap across the WGs. He recommended restoring or adding cross-cutting elements such as mental health to avoid a siloed approach.

Improving Data Collection

Dr. Saade recommended standardization and harmonization of records. The presenters highlighted roles for AI and ML approaches, all of which offer opportunities to improve prediction, prevention, and improved care. But large, well-curated datasets will be needed as input. Also critical is the need to be aware of potential bias of AI and ML approaches; researchers need to ensure that potential bias does not interfere with the outcomes.

AI natural language approaches might be able to provide "early warning scores," not just predictive approaches, that could improve pregnancy care overall, not just reduce stillbirth.

Enhancing Resources for Families Affected by Stillbirth

Prof. Lens remarked on the Australian Safer Baby Bundle and on care for parents who are dealing with the tragedy of stillbirth. She underscored the importance of individualized care, such as using the baby's name and respecting different experiences of grief. In some cultures, there is stigma around expressions of grief that need to be considered in the development of standards of care. Having such standards would likely help avoid situations in which trauma is compounded by mistreatment. Prof. Lens said that increased access to autopsy could help reduce self-blame.

Prof. Lens emphasized the importance of raising awareness about stillbirth: Most people do not understand that stillbirth still happens, even in high-income countries. She also mentioned a research gap: Little is known about the care people receive when they experience a stillbirth. SOARS data are available from two states, but a significant opportunity could be realized by implementing the tool in other states.

Concluding Remarks and Adjournment of Open Session

Lucky Jain, M.D., Co-chair, Emory University School of Medicine, Department of Pediatrics

Uma Reddy, M.D., M.P.H., Co-chair, Columbia University Irving Medical Center; Representative, ACOG

Dr. Jain thanked Dr. Bianchi, Dr. Williams, contractors, and NICHD staff for organizing a successful meeting and for the work already accomplished. He also thanked the presenters, especially international researchers, clinicians, and public health experts who have shared their experiences reducing stillbirths in their nations.

Dr. Jain said he looks forward to seeing the WG develop a solid report to present to the Advisory Council based on a strong resolve to reduce stillbirths in the United States.

Dr. Reddy added her thanks to NICHD, the presenters, and the WG members. The discussions, she said, have been particularly helpful. In terms of next steps, the WG will produce a report to present to the NACHHD Council during its meeting on June 3–4, 2024.

Dr. Williams adjourned the public meeting at 3:35 p.m.

Closed Session

Dr. Williams announced that the WG will meet again on February 20, 2024, to plan the drafting of the report. The tentative time for the meeting is 10 a.m. to 2 p.m., though that may change when the agenda is finalized. The meeting will be a closed session for the members, NICHD staff, and ad hoc contractors.

Dr. Williams anticipates that the WG will meet again in mid-April to review the draft report. She said that the plan is to present the preliminary findings to the NACHHD Council during its meeting on June 3–4, 2024.

Dr. Williams adjourned the closed session at 3:38 p.m.