Clinical Research Design and Standards of Care for the Intervention and Prevention of Stillbirth and Adverse Pregnancy Outcomes as Recommended by ACOG: A Literature Review

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Every year in the United States, about 21,000 babies are stillborn - a number that the NIH has called “unacceptably high[1].” The rate of stillbirth is higher in the United States than it is in 25 other high income countries[2]. Due to a lack of awareness on the risks associated with stillbirths and minimal research on prevention methods for these risks, fetal mortality remains a major public health concern. Additionally, for fetal mortality risk factors that are known and can be addressed, interventions have yet to be developed and tested in a clinical setting. This literature review was performed to describe current guidelines for the prevention of fetal mortality as endorsed by the American College of Obstetricians and Gynecologists - the nation’s leading organization for OBGYNs - (ACOG), the clinical evidence ACOG has used to base their recommendations on, and future directions for clinical studies on stillbirth prevention and intervention. We found that because of the risks and ethical considerations involved in randomized control trials studying the effects of stillbirth prevention interventions, ACOG rarely makes evidenced-based recommendations. However, this review will be used in the design of a clinical study for the organization Measure the Placenta that aims to estimate the clinical utility of Estimated Placental Volume (EPV) prevention of fetal mortality.

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[1] Eldeib D. Federal Study Calls U.S. Stillbirth Rate “Unacceptably High” and Recommends Action. ProPublica. Accessed May 11, 2023. https://www.propublica.org/article/stillbirths-rate-nih-cdc-prevention-research

[2] Stillbirth Working Group of Council | NICHD - Eunice Kennedy Shriver National Institute of Child Health and Human Development. www.nichd.nih.gov. Accessed May 11, 2023. https://www.nichd.nih.gov/about/advisory/council/stillbirth-working-group-of-council

Placenta Volume as a Risk and Overview of EPV

Given that extremes of placental weight have been found to be associated with stillbirth and other adverse perinatal outcomes (independent of birth weight[3]) monitoring fetal movement during pregnancy could help identify at-risk fetuses. Abnormal placental weight and birth weight:placental weight ratios have been significantly linked[4] to adverse pregnancy outcomes; high fetal:placental weight ratios have been associated with adverse birth outcomes due to fetuses outgrowing their placentas, such that smaller placentas[5] have been associated with these adverse outcomes. Therefore, it is crucial to closely monitor and manage pregnancies[6] with abnormal placental weights or birth weight:placental weight ratios to reduce the risk of potential stillbirths.

Understanding the relationship between placental weight and adverse pregnancy outcomes, such as stillbirth, is crucial for identifying and managing at-risk pregnancies. By implementing strategies to monitor fetal growth and placental function, healthcare providers can work to reduce the incidence of stillbirth. Fortunately, the use of two-dimensional ultrasound technology[7] can accurately predict placental weight through the use of EPV calculations. These calculations are valid in different populations[8], at various gestational ages, and match the placental parabolic growth curve described in other publications. By establishing EPV growth curves[9], similar to

[3] Hutcheon, J.A., et al., 2012. Placental weight for gestational age and adverse perinatal outcomes. Obstetrics & Gynecology, 119(6), pp.1251-1258.
[4] Campbell, J., et al., 2020. Normally Grown Non-dysmorphic Stillbirth Post 38 Weeks Gestation and Reduced Fetal Movements: A Matter of Reserve? A Retrospective Study. Journal of Fetal Medicine, 7(2), pp.111-117.
[5] Higgins, L.E., et al., 2015. Placental features of late-onset adverse pregnancy outcome. PloS One, 10(6), p.e0129117.
[6] Dypvik, J., et al., 2020. Placental weight and risk of neonatal death. JAMA Pediatrics, 174(2), pp.197-199.
[7] Azpurua, H., et al., 2010. Determination of placental weight using two-dimensional sonography and volumetric mathematic modeling. American Journal of Perinatology, 27(02), pp.151-155.
[8] Isakov, K.M., et al., 2018. Estimated placental volume and gestational age. American Journal of Perinatology, 35(08), pp.748-757.
[9] Arleo EK, Troiano RN, da Silva R, Greenbaum D, Kliman HJ. Utilizing two-dimensional ultrasound to develop normative curves for estimated placental volume. American journal of perinatology. 2014;31(8):683–8. pmid:24108663.

fetal and pediatric growth charts, providers are able to better detect outliers and concerning trends in placental size and function. This allows for more effective risk stratification of prenatal patients, and ultimately helps to reduce the incidence of adverse perinatal outcomes.

Current Barriers to Collecting Data

Despite advances in obstetric care and research, collecting accurate and comprehensive data on stillbirths can be challenging for several reasons. The prevalence of stillbirth can challenge clinical research given that stillbirth is a comparatively less frequent event to other perinatal outcomes, such as live births or neonatal deaths, varying across different populations and geographic regions – meaning that large sample sizes are needed to conduct meaningful research studies. Furthermore, the low prevalence of stillbirth can also impact the statistical power of studies. If a study has a small sample size, there may not be enough statistical power to detect meaningful differences between groups or to identify significant associations between variables.

In addition, the lack of standardization in definitions and reporting criteria for stillbirth can make it difficult to compare data across studies and populations. Variation exists at the local and state level. Each state has its own definition of stillbirth, which can lead to inconsistencies in data collection[10] and reporting[11]. For example, some states define stillbirth as the loss of a fetus after 20 weeks of gestation, while others use different criteria, such as weight or gestational age. This lack of standardization can make it difficult to compare data across states and regions. Stillbirth data is typically collected by state health departments, but not all states have robust systems in

[10] Tavares Da Silva F, Gonik B, McMillan M, Keech C, Dellicour S, Bhange S, Tila M, Harper DM, Woods C, Kawai AT, Kochhar S, Munoz FM; Brighton Collaboration Stillbirth Working Group. Stillbirth: Case definition and guidelines for data collection, analysis, and presentation of maternal immunization safety data. Vaccine. 2016 Dec 1;34(49):6057-6068. doi: 10.1016/j.vaccine.2016.03.044. Epub 2016 Jul 16. PMID: 27431422; PMCID: PMC5139804.

[11] Flenady V, Wojcieszek AM, Middleton P, Ellwood D, Erwich JJ, Coory M, et al. Stillbirths: recall to action in high-income countries. Lancet. 2016 Feb 13;387(10019):691-702. doi: 10.1016/S0140-6736(15)01020-X. PMID: 26794078.

place for tracking this information[12]. Furthermore, access to this data can be limited due to privacy concerns or other bureaucratic barriers.

Underreporting of stillbirths is another major challenge in collecting data on stillbirths in the United States. Many stillbirths go unreported, particularly those that occur before 20 weeks of gestation or outside of a healthcare facility[13]. This can lead to significant underestimation of the true incidence of stillbirth. Furthermore, some families may choose not to report a stillbirth due to stigma or cultural barriers, which can also contribute to underreporting.

Lack of funding is another barrier to collecting comprehensive data on stillbirths. There is often limited funding available for stillbirth research and data collection, which can make it difficult to establish and maintain robust systems for tracking this information[14]. This lack of funding can also limit the development of new interventions or treatments for stillbirth, which can perpetuate the problem.

Finally, stigma and cultural barriers can also hinder efforts to collect accurate and comprehensive data on stillbirths in the United States. There can be cultural and societal barriers that prevent families from reporting stillbirths or discussing them openly[15]. In some cases, stillbirth may be viewed as a taboo topic, which can lead to shame or isolation for

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[12] Auger N, Bilodeau-Bertrand M, Poissant J, Shah PS. Decreasing use of autopsy for stillbirths and infant deaths: missed opportunity. J Perinatol. 2018 Oct;38(10):1414-1419. doi: 10.1038/s41372-018-0191-y. Epub 2018 Aug 3. PMID: 30076403.

[13] Reinebrant, HE, Leisher, SH, Coory, M, Henry, S, Wojcieszek, AM, Gardener, G, Lourie, R, Ellwood, D, Teoh, Z, Allanson, E, Blencowe, H, Draper, ES, Erwich, JJ, Frøen, JF, Gardosi, J, Gold, K, Gordijn, S, Gordon, A, Heazell, AEP, Khong, TY, Korteweg, F, Lawn, JE, McClure, EM, Oats, J, Pattinson, R, Pettersson, K, Siassakos, D, Silver, RM, Smith, G, Tunçalp, Ö, Flenady, V. Making stillbirths visible: a systematic review of globally reported causes of stillbirth. BJOG 2018; 125: 212– 224.

[14] Frøen JF, Friberg IK, Lawn JE, Bhutta ZA, Pattinson RC, Allanson ER, et al. Stillbirths: progress and unfinished business. Lancet. 2016 Feb 6;387(10018):574-586. doi: 10.1016/S0140-6736(15)00818-1. PMID: 26794081.

[15] Cacciatore J, Blood C, Kurker S. From ‘‘Silent Birth’’ to Voices Heard: Volunteering, Meaning, and Posttraumatic Growth After Stillbirth. Illn Crisis Loss. 2018;26(1):23-39. doi: 10.1177/1054137317740799.

families who have experienced this type of loss. This stigma can also contribute to underreporting and a lack of understanding of the true scope of the problem.

On Disparities

In their seminal work, the Centers for Disease Control and Prevention (CDC) reports[16] that certain racial and ethnic groups have a higher risk of stillbirth compared to others. For instance, Native Hawaiian or Other Pacific Islander pregnancies have a 1 in 94 chance of ending in stillbirth, while Asian pregnancies have a 1 in 254 chance. Black pregnancies have a 1 in 97 chance, compared to Hispanic and White pregnancies with a 1 in 205 and 1 in 211 chance, respectively. These disparities in stillbirth rates highlight the need for clinical research to address these health inequities. To address these disparities, clinical research must prioritize engagement with diverse communities. Researchers can work to engage with communities that experience disparities in health outcomes to understand their perspectives, concerns, and priorities. This can help to develop research questions that are relevant and meaningful to these communities. It is essential to involve these communities in the research process, from study design to dissemination of findings, to ensure their voices are heard and their needs are addressed. Incorporating diversity in study participants is also crucial in addressing disparities in health outcomes. Studies should include a diverse group of participants that represent the population being studied. This can be achieved by intentionally recruiting participants from underrepresented communities and considering factors such as race, ethnicity, socioeconomic status, and geography. By ensuring a diverse study population, clinical researchers can better understand the impact of social determinants of health and identify potential interventions to address these disparities.

[16] Pruitt SM, Hoyert DL, Anderson KN, et al. Racial and Ethnic Disparities in Fetal Deaths — United States, 2015–2017. MMWR Morb Mortal Wkly Rep. 2020;69:1277-1282. doi: 10.15585/mmwr.mm6937a1.

Current Guidelines and Information Available through ACOG on the Management and Prevention of Stillbirth

The American College of Obstetricians and Gynecologists is the largest professional organization of doctors that specialize in birth and delivery. According to their clinical website, which was last updated in 2020, stillbirth is defined as "the delivery of a fetus showing no signs of life as indicated by the absence of breathing, heartbeats, pulsation of the umbilical cord, or definite movements of voluntary muscles[17]." Because stillbirth cannot be diagnosed until after the death of the fetus, all of the recommendations for the management of fetal death from the ACOG clinical site involve post-delivery actions. These include autopsy of the fetus and examination of the placenta and umbilical cord, among other recommendations. While these assessments are helpful in collecting data to evaluate for potential causes, nowhere does the organization make recommendations for doctors on the prevention of stillbirth. On the "for patients" version of the ACOG website, very vague information can be found on the topic of diagnosis recommendations. An ultrasound to detect the fetal heartbeat and continuous monitoring of the fetus with electronic fetal monitoring are seemingly the only options for patients as recommended by ACOG[18]. Overall, this leading professional organization has minimal resources for patients and providers on their main stillbirth websites.

According to the ACOG patient website, electronic fetal monitoring (EFM) is a current standard of care to prevent stillbirth through monitoring of the fetus in a high risk pregnancy (18). EFM was first described in 1931 and made commercially viable and available in 1967[19]. This means that EFM was used in the clinic a decade before randomized control trials were available.

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[17] Management of Stillbirth. www.acog.org. https://www.acog.org/clinical/clinical-guidance/obstetric-care-consensus/articles/2020/03/management-of-stillbirth

[18] Stillbirth. www.acog.org. https://www.acog.org/womens-health/faqs/stillbirth

[19] History of Fetal Monitoring – Electronic Fetal Monitoring. Accessed May 11, 2023. https://ob-efm.com/efm-basics/history/#:~:text=Electronic%20Fetal%20Monitoring

Currently, RCTs have studied the success of EFM in comparison to other technologies, but the efficacy of EFM has never been studied on its own. Standards for EFM were not declared by ACOG until 1997, despite its use clinically for decades prior. While 85% of deliveries today use electronic fetal monitoring, EFM does not appear to improve outcomes and many doctors remain wary on its recommendation from ACOG[20]. It remains unclear where the evidence for EFM as a standard of care came from.

In June 2021, ACOG released a committee opinion on indications for outpatient antenatal fetal surveillance, a method used for reducing the risk of stillbirth in high-risk pregnancies[21]. Antenatal fetal testing is defined as "fetal surveillance used to indirectly evaluate the fetal status[22]." The goals of surveillance are to identify fetuses at risk of stillbirth and intervene prior to adverse outcomes. Some of these testing and surveillance techniques include fetal movement awareness, nonstress test, contraction stress test, biophysical profile, and umbilical artery doppler velocimetry[23]. Throughout the committee opinion document, it's made abundantly clear that the guidance "should only be considered as suggestions, not mandates or all encompassing" (5). This is due to the "paucity of evidence for the efficacy of antenatal fetal surveillance and for evidence-based recommendations" (5). The document alludes to a few prospective and observational studies, including some performed in other countries, but no

[20] Is electronic fetal monitoring worthwhile? | Your Pregnancy Matters | UT Southwestern Medical Center. utswmed.org. Accessed May 11, 2023. https://utswmed.org/medblog/electronic-fetal-monitoring-high-risk-pregnancy/#:~:text=For%20high%2Drisk%20pregnancies%2C%20in

[21] Driggers W, Bryant A, Ghidini A. ACOG COMMITTEE OPINION Number 828 Committee on Obstetric Practice Society for Maternal-Fetal Medicine This Committee Opinion Was Developed by the Committee on Obstetric Practice in Collaboration with Committee Members Rita the Society for Maternal-Fetal Medicine in Collaboration With. Accessed May 11, 2023. https://www.acog.org/-/media/project/acog/acogorg/clinical/files/committee-opinion/articles/2021/06/indications-for-outpatient-antenatal-fetal-surveillance.pdf

[22] Signore C, Freeman RK, Spong CY. Antenatal Testing—A Reevaluation. Obstetrics and Gynecology. 2009;113(3):687-701.

[23] Sienas L, Napolitano P, Delaney S. Antepartum Outpatient Fetal Testing Obstetric Consensus Conference.; 2020. Accessed May 11, 2023. https://www.uwmedicine.org/sites/stevie/files/2020-08/Antenatal%20Outpatient%20Testing%20-%202020_2.pdf

randomized control trials. While it is noted that the recommendations in the committee opinion were put together with the help of experts in the field, it is mostly unclear what evidence base ACOG has for recommendations for surveillance. Many of the conditions in the document which would warrant antenatal fetal surveillance conclude with something similar to the paragraph on tobacco use: “for pregnant patients who smoke cigarettes and e-cigarettes, there is insufficient evidence to recommend routine antenatal fetal surveillance” (5). Interestingly, the document does discuss placenta size as a risk factor for stillbirth, noting that almost 25% of stillbirths in the US are preventable, with 57% of them due to placental abnormalities (5). However, the recommendation of antenatal fetal monitoring from ACOG comes only in the instances of velamentous cord insertion or single umbilical artery. The stillbirth rates for these conditions were 34 in 1000 and 12 in 1000, respectively. Stillbirth rates and odds ratios for velamentous cord insertion and single umbilical artery were determined through case control studies and meta analyses, but in neither case has antaneal fetal surveillance been utilized or tested as an intervention. Again, it is unclear where the recommendation for surveillance specifically for these placental abnormalities comes from, especially in comparison to any other placental abnormality. The guidance document includes a paragraph on future research to be done, essentially stating that more research needs to be done on interventions such as antenatal fetal surveillance but there are many challenges in doing so, including “randomizing tens of thousands of pregnant individuals (...) to develop evidence-based recommendations”. The frequent mention of evidence-based recommendations is inconsistent with the recommendations that ACOG has provided, which have very little evidence to support them. In conclusion, when ACOG sets standards of care such as antenatal fetal surveillance, the guidance is very loosely based on clinical studies and data and is likely motivated by external stakeholders rather than evidence.

In a similar document from the University of Washington, titled Antepartum Outpatient Fetal Testing, the different types of antenatal fetal testing, surveillance, and clinical recommendations are outlined and in conjunction with the committee opinion from ACOG. They note “there have been no randomized controlled trials that prove the effectiveness of any antepartum fetal surveillance, further proving the lack of evidence used in the original committee opinion. They write that the clinical impact of these tests comes from “untested historical controls with the same indications for testing and the contemporary untested general low risk population.” In a table demonstrating the negative predictive value and false positive rates of nonstress test, biophysical profile, modified biophysical profile, and contraction stress test, the negative predictive value (defined as the likelihood that a person who has a normal test result does not give birth to a stillborn child within one week) for all four tests is 99.8% or higher. However, all of the tests have a false positive rate (defined as the number of false tests wrongly categorized as positive) that is greater than 30%. For the nonstress test, the false positive rate went up to 90%. Not only could a false positive for an antenatal fetal test lead to negative consequences like maternal stress, which could further manifest as fetal mortality, but the cost and time that will be wasted from further testing and medical care is enormous. Further, the authors note that because antenatal fetal surveillance is already in practice, randomized control trials are unlikely to ever be done to prove efficacy of these types of testing and surveillance. Performing a randomized control trial now would require randomization away from the normative practice, which obviously brings ethical implications into play. In addition to questionable efficacy of the tests themselves, throughout the literature there is no evidence of one antenatal testing strategy demonstrating superior efficacy over another. Again, this is due to a lack of randomized control trials among pregnant women.

Published Studies Focused on the Intervention and Prevention of Stillbirth and Adverse Pregnancy Outcomes

Very little research has been or is being done on interventions for risk factors related to fetal mortality. For the studies that have produced results, the findings are often weak and lack evidence to support the intervention. A systematic review was performed in 2020 on all Cochrane reviews globally that included randomized controlled trials (RCTs) of antepartum interventions aiming to prevent stillbirth, perinatal mortality, and fetal death[24]. The 43 reviews that met the systematic review inclusion criteria contained 61 different interventions and were classified based on the effectiveness of the intervention at preventing stillbirth. Interventions were grouped into four different categories: nutrition, preventing infection, managing maternal healthcare problems, and checking the fetus before birth. For the purposes of this literature review focused on placental volume, only interventions in the category focused on screening and management of fetal growth and well-being will be discussed. The authors found only one out of the seven systematic reviews reported an intervention that showed clear evidence of benefit in reducing stillbirth risk (which was the primary outcome in this paper), which was all routine Doppler ultrasound versus no routine Doppler ultrasound. The interventions which did not have enough evidence to support them were as follows: routine ultrasound after 24 weeks versus no/selective ultrasound after 24 weeks, all routine Doppler ultrasound versus no Doppler ultrasound (fetal/umbilical vessels + uterine artery), single Doppler ultrasound assessment versus no Doppler ultrasound (fetal/umbilical vessels only), multiple Doppler ultrasound assessments versus no Doppler ultrasound (fetal/umbilical vessels + uterine artery, fetal movement counting versus hormonal analysis, and utero-placental doppler ultrasound versus no ultrasound, second trimester. The secondary outcome of perinatal death again had only one intervention with clear evidence to support its use: computerized antenatal CTG versus traditional antenatal CTG. Again, eight interventions had little to no evidence of benefit to prevention of perinatal death. This is not to say the interventions have no clinical benefit, but

[24] Ota E, da Silva Lopes K, Middleton P, et al. Antenatal interventions for preventing stillbirth, fetal loss and perinatal death: an overview of Cochrane systematic reviews. Cochrane Database of Systematic Reviews. Published online December 18, 2020. doi:https://doi.org/10.1002/14651858.cd009599.pub2

that the studies reviewing the interventions did not contain enough information or a high enough quality of evidence to understand the association between the intervention and its effects and therefore make evidence-based recommendations for standards of care. In some cases, the studies did not have large enough cohorts, the results were estimated to be highly biased, or the studies were so old that they could not be generalized to today's standards of care. The authors conclude that "most interventions were unable to demonstrate a clear effect in reducing stillbirth or perinatal death" and "research efforts should be focused on high-quality RCTs to evaluate the effects of prevention interventions". They also note that because stillbirths are more common among low income communities, interventions should especially be conducted among that population.

There are a few recent randomized control trials involving pregnant women. One that was endorsed by ACOG and became a model for clinical guidance is the ARRIVE trial, which compared labor induction versus expectant management in low-risk nulliparous women[25]. On the ACOG clinical website, there is a message that states "this information is designed as an educational resource to aid clinicians in providing obstetric and gynecologic care, and use of this information is voluntary[26]." Again, the organization does not take a strong stance in making an evidence-based recommendation. In any case, the design of the trial was multicenter, with 41 participating hospitals, with 50,851 women screened and 6106 providing written consent and participating in randomization. Women were randomized to an induction group - assigned to undergo induction of labor at 39 weeks 0 days to 39 weeks 4 days, or an expectant-management group - asked to forego elective delivery before 40 weeks 5 days and to

[25] Grobman WA, Rice MM, Reddy UM, et al. Labor Induction versus Expectant Management in Low-Risk Nulliparous Women. N Engl J Med. 2018;379(6):513-523. doi:10.1056/NEJMoa1800566
[26] Clinical Guidance for Integration of the Findings of The ARRIVE Trial: Labor Induction Versus Expectant Management in Low-Risk Nulliparous Women. www.acog.org. https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2018/08/clinical-guidance-for-integration-of-the-findings-of-the-arrive-trial

have delivery initiated no later than 42 weeks 2 days. The primary outcome was perinatal mortality or severe complications. Secondary outcomes were split into neonatal (birthweight, hyperbilirubinemia, blood transfusion, etc.) and maternal (cesarean section, postpartum hemorrhage or infection, number of hours in labor, maternal death, etc.). The results showed elective labor induction at 39 weeks of gestation did not result in a greater frequency of perinatal adverse outcomes than expectant management and resulted in fewer instances of cesarean delivery. As a result, ACOG states in the practice bulletin that "it is reasonable for obstetricians and health-care facilities to offer elective induction of labor to low-risk nulliparous women at 39 weeks gestation". It is likely that ACOG promoted this clinical study and used it to make an evidence-based recommendation over other clinical studies because of the low-risk nature of the study cohort. ACOG is specific in making their recommendation only for pregnant patients that match the cohort and implying that the study does not generalize to a greater population. However, the size and methods of the trial are useful in understanding what studies ACOG sees as a successful clinical study model.

Another trial assessing pregnancy outcomes with published results on the ACOG website is the chronic hypertension and and pregnancy (CHAP) multi-center randomized control trial[27]. While not directly related to interventions to decrease the risk of stillbirth, the study again provides insight on what ACOG finds a feasible trial to inform their evidence-based decision making. Among 70 sites, 29,772 patients were screened, which resulted in a cohort of 2408 women with a known or new diagnosis of mild chronic hypertension and a singleton pregnancy before 23 weeks of gestation who were enrolled in the trial to assess the benefits and safety of

[27] Clinical Guidance for the Integration of the Findings of the Chronic Hypertension and Pregnancy (CHAP) Study. www.acog.org. https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2022/04/clinical-guidance-for-the-integration-of-the-findings-of-the-chronic-hypertension-and-pregnancy-chap-study

antihypertensive treatment during pregnancy[28]. Patients in the treatment group were prescribed an antihypertensive drug specifically for pregnancy and the control group received routine care of withholding therapy unless hypertension developed. There were a few primary outcomes measured: preeclampsia, medically induced preterm birth, placental abruption, and fetal death. The primary safety outcome was fetal growth and secondary outcomes included maternal death or complications, preterm birth, and various neonatal complications. The authors found that antihypertensive treatment for women with a blood-pressure target of less than 140/90 mm Hg improved pregnancy outcomes with no apparent harm to the fetus, with women receiving treatment having a lower risk of one or more of the primary outcomes assessed (12). Based on this study, ACOG recommendations became “utilizing 140/90 as the threshold for initiation or titration of medical therapy for chronic hypertension in pregnancy, rather than the previously recommended threshold of 160/110” (11). This study differs from the ARRIVE trial in that the pregnant women involved in the CHAP trial were not necessarily low risk, and all had a risk factor of hypertension in their pregnancy. Because there was a protocol deviation that if a woman in the control group were to experience hypertension, she should begin taking antihypertensive medication, ethical implications that could have arisen in the trial were subsided.

A recent RCT that assessed a stillbirth prevention intervention method was the My Baby’s Movements trial, performed in Australia[29]. Again a multicenter trial involving 27 centers, the study cohort contained 290,105 eligible women who were randomized into clusters. Women were given a package of interventions to increase decreased fetal movement awareness, with the clusters receiving the package at different time points. The inclusion criteria for this study

[28] Tita AT, Szychowski JM, Boggess K, et al. Treatment for Mild Chronic Hypertension during Pregnancy. The New England Journal of Medicine. 2022;386. doi:https://doi.org/10.1056/NEJMoa2201295

[29] Flenady, V et al. “My Baby's Movements: a stepped-wedge cluster-randomised controlled trial of a fetal movement awareness intervention to reduce stillbirths.” BJOG : an international journal of obstetrics and gynaecology vol. 129,1 (2022): 29-41. doi:10.1111/1471-0528.16944

was a little bit more loose, with a pregnant woman in a singleton pregnancy with no lethal fetal congenital anomalies past 28 weeks being eligible to participate. In this study, every maternity center received the intervention package, but clusters of centers were given the intervention at different time points. The package consisted of education for the clinical site team, awareness raising materials, an eLearning program via app or text message. The primary outcome was stillbirth rates and secondary outcomes included induction of labor, birth size, cesarean section, and adverse neonatal outcome measures. While the intervention group saw a slight decrease in stillbirth rates (2.2/1000 versus 2.4/1000), the result was not statistically significant, but the authors suggest that increased clinician awareness of decreased fetal movement along with early reporting from pregnant women thanks to the eLearning program were responsible for the increase in intervention strategies for reducing stillbirth (12). The decrease in stillbirth rate was greater across calendar time: 2.7/1000 in the first versus 2.0/1000 in the last 18 months. Overall, this trial successfully incorporated both physician and patient education on a risk for stillbirth and demonstrated potential success for future trials for high-risk pregnancy interventions. However, it is difficult to ascertain whether women or clinicians were already aware of the risks of decreased fetal movement prior to intervention. Also, hospital effects were taken into account in the results of the study, but it is impossible to remove all of the confounding effects.

Two other studies have demonstrated the effects of intervention on decreased fetal movement, with mixed results: the Mindfetalness study and the AFFIRM trial. The Mindfetalness study focused their intervention solely on pregnant women, with women being randomized to receive either a pamphlet about fetal movements and the Mindfetalness method or routine care. The cohort spanned 67 care clinics in Sweden with 39,865 women participating[30]. Using an apgar

[30] Akselsson A, Lindgren H, Georgsson S, et al. Mindfetalness to increase women's awareness of fetal movements and pregnancy outcomes: a cluster‐randomised controlled trial including 39 865 women. BJOG: An International Journal of Obstetrics & Gynaecology. 2020;127(7):829-837. doi:https://doi.org/10.1111/1471-0528.16104

score, which measures the baby's well being afterbirth, as a measure for the success of the intervention, they found no significant difference among groups. However, they did find an increase in multiple health benefits, including a decreased incidence of cesarean section, fewer children born small-for-gestational-age and fewer children born after gestational week 41 among women who were given the Mindfetalness intervention, demonstrating that the method did help improve outcomes for pregnant women (14). These results showed a contrast to the AFFIRM trial, which focused on educating both healthcare professionals and pregnant women in the UK and Ireland. In this trial, the intervention package included an eLearning module for clinical staff in participating hospitals, including a management plan for delivery of babies at high risk, and a pamphlet for pregnant women on the risks of reduced fetal movement (RFM). The primary outcome was the incidence of stillbirth, with secondary outcomes of cesarean section, induction of labor, admissions to NICU, among others. In the 37 hospitals included in the study, 409,175 women participated over the two year study period[31]. An interesting part of the study design was the cluster method, which "allows interventions to be implemented at a hospital or regional level and minimizes contamination between groups, which might occur if clinicians have to provide different standards of care to different women on the same day (14)." However, the AFFIRM trial not only found no significant improvements in stillbirth outcomes (a minor reduction of 44/10,000 in the intervention group versus 41/10,000 in the control group) and saw a significant increase in the frequency of induction of labor and cesarean section. The authors concluded that awareness of RFM alone is not enough to improve stillbirth rates.

In Germany, a smaller multicenter randomized control trial (the SAFE trial) among pregnant women set out to determine which method of measuring amniotic fluid volume proved to be

[31] Norman JE, Heazell AEP, Rodriguez A, et al. Awareness of fetal movements and care package to reduce fetal mortality (AFFIRM): a stepped wedge, cluster-randomised trial. The Lancet. 2018;392(10158):1629-1638. doi:https://doi.org/10.1016/s0140-6736(18)31543-5

more efficacious: amniotic fluid index (AFI) or single deepest vertical pocket (SDP)[32]. Both techniques are used in measuring amniotic fluid and can result in a cesarean section for delivery if decreased amniotic fluid volume is diagnosed at term. Typically AFI overestimates amniotic fluid volumes and SDP underestimates volume, with both being poor predictors of amniotic fluid adequacy. Four university hospitals were involved and women with a singleton pregnancy in cephalic presentation at greater than 259 days of gestation (at term) in both high and low risk pregnancies were eligible, resulting in a cohort of 1052 women. A high risk pregnancy was defined as one with the presence of gestational diabetes, hypertensive disorder, fetal growth restriction, placental insufficiency, or intrahepatic cholestasis of pregnancy. The primary outcome was postpartum admission to the NICU and secondary outcomes were fetal death, induction of labor, and cesarean section among others. Results found no significant difference between NICU admissions among either group, but an increase in the diagnosis of oligohydramnios in the group that received AFI, resulting in more inductions of labor in this group (15). The authors concluded that the SDP technique is more favorable to estimate amniotic fluid volume, especially in low-risk pregnancies. While this RCT did not have very significant findings, it is an interesting design that incorporates both high and low risk pregnancies.

Advocacy Strategy

Advocacy efforts should be made to demand more research and greater transparency from organizations like the American College of Obstetricians and Gynecologists (ACOG) in how they set standards of care for pregnancy management. One way to build momentum for stillbirth advocacy is through publishing opinion editorials. By writing and publishing pieces in reputable

[32] Kehl, S et al. “Single deepest vertical pocket or amniotic fluid index as evaluation test for predicting adverse pregnancy outcome (SAFE trial): a multicenter, open-label, randomized controlled trial.” Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology vol. 47,6 (2016): 674-9. doi:10.1002/uog.14924

publications, advocates can raise awareness about stillbirth and the need for more research. These pieces can also demand greater transparency from organizations like ACOG in how they set standards of care for pregnancy management. By bringing attention to these issues, opinion editorials can help build momentum for stillbirth advocacy efforts.

In addition, collaborations with the National Institute of Child Health and Human Development (NICHD) have been proposed as a way to hold organizations accountable for their commitments to stillbirth research. Working with the NICHD, for example, can provide a platform for advocates to engage with experts in the field of stillbirth research. Collaboration can also hold organizations accountable for their commitments to more research. By working with the Stillbirth Working Group of Council, advocates can help guide and shape the research agenda to address the critical gaps in knowledge about stillbirth. Advocating for changes to standards of care and transparency from organizations like ACOG is essential to reducing the incidence of stillbirth and improving pregnancy outcomes. Building momentum through publishing opinion editorials and collaborating with organizations like NICHD and the Stillbirth Working Group of Council can help hold organizations accountable and guide the research agenda to address the critical gaps in knowledge about stillbirth.

The Stillbirth Working Group of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Council, composed of members from government, academia, and advocacy groups, released a report in 2023 containing recommendations for reducing stillbirth rates in the US. In recognizing stillbirth as a significant public health concern, they emphasized the need for increased research, prevention, and support for affected families; they underscored the importance of improving data collection and surveillance systems to accurately measure stillbirth rates and identify risk factors. Additionally, the working group emphasized the importance of advancing research in stillbirth prevention and treatment. Among

these recommendations were three focused on research on prevention and intervention: NIH should convene a group of basic, translational, clinical, and public health research experts, as well as parents who have experienced stillbirth, to develop a research agenda to advance prevention for stillbirth and other adverse pregnancy outcomes; NIH should conduct or support research to establish baseline normative data on physiology in pregnancy, including potential indicators of health and disease; and NIH and CDC should support additional research on causes and risk factors, as well as prevention of stillbirth more broadly[33]. They highlighted the need for innovative approaches, including studying placental health, genetic factors, and maternal-fetal interactions to better understand the causes and potential interventions for stillbirth. After discussing the significance of prenatal care and the role it plays in preventing stillbirths, they identified areas for further research to empower healthcare providers to identify and manage maternal conditions and factors that contribute to stillbirth risk, such as gestational diabetes, hypertension, and advanced maternal age, as well as placental volume and health. Organizations like the CDC and NIH, rather than ACOG, are looking to fund research initiatives to advance the standards of care. For instance, the CDC is currently supporting a trial with the Utah Department of Health and Human Services “to collect information on maternal experiences and behaviors prior to, during, and immediately following pregnancy among mothers who have recently experienced a stillbirth[34] called SOARS. The study involves collecting surveys from these mothers in hopes of finding clear risk factors associated with stillbirths. Finally, the group recognized the emotional toll of stillbirth on families and stressed the importance of providing comprehensive support services. They discussed the need for grief counseling, mental health support, and resources to help families cope with the loss of a baby.

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[33] Stillbirth Working Group of Council | NICHD - Eunice Kennedy Shriver National Institute of Child Health and Human Development. www.nichd.nih.gov. Accessed May 11, 2023. https://www.nichd.nih.gov/about/advisory/council/stillbirth-working-group-of-council

[34] Maternal and Infant Health Program. mihp.utah.gov. Accessed May 11, 2023. https://mihp.utah.gov/study-of-associated-risk-of-stillbirth

Conclusion

Stillbirth is a very prevalent and devastating public health issue, especially in the United States among marginalized communities. The American College of Obstetricians and Gynecologists has limited resources available for both clinicians and mothers on the prevention and management of stillbirth. The standards of care that are used and accepted in the field set forth by ACOG come with very little evidence to support them, yet ACOG claims they rely on clinical studies to make evidence-based decisions. Research on stillbirth interventions has been minimal even on a global scale, but successful clinical trials have been multicenter randomized control trials that deliver an entire intervention package, including an education component for both mothers and clinicians. Continuous advocacy work and research through the support of CDC, NIH, and the Stillbirth Working Group can lead the path to changing the standards of care with efficacious interventions.