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REPRODUCTIVE AND PERINATAL EPIDEMIOLOGY (EF SCHISTERMAN, SECTION EDITOR)

Congenital Malformations and Consequential Epidemiology

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Abstract A call for a shift in the discipline of epidemiology, away from those aimed at identifying risk factors and toward those aimed at more directly improving health, is the so-called c*onsequential epidemiology*. This call for epidemiologists to engage in solving the biggest public health problems has been heralded for decades by Cates and more recently by Galea [Am J Epidemiol 178: 1185–94, 2013]. In consideration of the consequential epidemiology perspective, the impacts of epidemiologic research of birth defects over the recent decades are evaluated and directions for the field are proposed. While many causal factors have been identified, the causes of the majority of birth defects remain unknown. Folic acid intake notwithstanding, primary prevention of birth defects is elusive. Meanwhile, research that identifies what improves the lives of individuals born with a birth defect and how to ensure those factors are available to all affected would have great impact. In summary, a consequentialist approach to birth defects epidemiology requires a shift in research agendas and teams, but the opportunities are wide open.

Keywords Future · History · Birth defects · Risk factors · Access to care · Quality of life

Introduction

Galea and Cates argue for an emphasis shift in epidemiology, away from etiologic studies and toward studies that identify direct improvements in population health and that evaluate how to implement those improvements. This more public health practice-based focus for epidemiology has been labelled consequentialist epidemiology [1••, 2••]. Their call is based on reflections of public health achievements in epidemiology over the past decades and on acknowledgement of the current and future contexts in which epidemiology sits. Galea and Cates [1••, 2••] point out the relative lack of attention that has been paid in recent decades to solving large-scale public health problems, such as those in developing countries, and they identify current and future decreases in public research funds (e.g., lower NIH paylines) and societal changes (e.g., US health-care systems and widening income gaps). Epidemiology is a broad discipline, and thus, Galea and Cates' points deserve consideration within substantive areas of the field. Here, I reflect on epidemiologic research of birth defects over the recent decades and propose directions for the field from a consequentialist perspective.

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History

One of the greatest epidemiologic discoveries and public health actions to date—prevention of neural tube defects with folic acid—is a proud accomplishment of birth defect epidemiologists and one with clear consequences. An estimated 500 cases of spina bifida and anencephaly are prevented annually in the USA and Canada as a result of folic acid fortification of cereal grains [3, 4]. The evidence to support such a major public health intervention came from a randomized, controlled, double-blind clinical trial [5] and several observational studies [6–10] conducted in the 1980s and 1990s. Aside from the folic acid success story, experimental approaches to study potential preventative measures of birth defects are particularly complicated in pregnant populations because meeting the principles of a favorable balance of

benefits and risks can be difficult to achieve when both mother and fetus must be considered [11].

Over the past decades, birth defects epidemiology has experienced an enormous boom, with many more observational studies and substantial improvements in design, exposure and outcome measurement, and analytic methods such as modeling. Formal epidemiologic studies with structured data collection and control groups replaced reports on clinical series that had previously dominated the field. Outcome definitions have also become more specific and etiologically meaningful. Collectively, birth defects affect approximately 3 % of live births, but when looking for causal factors, grouping all congenital structural anomalies together is analogous to grouping all neoplasms together. Descriptive epidemiology shows quite different patterns of occurrence for specific defects, according not only to organ system affected (e.g., musculoskeletal) but also the structure (e.g., limb), subtype of limb defect (e.g., terminal transverse deficiency), and presence of associated anomalies (e.g., terminal transverse limb deficiency with absent pectoralis muscle). As the birth defect epidemiologist drills down to more detailed phenotypes, the etiology is presumed to be more homogeneous, but the frequency of occurrence decreases. Thus, cohort studies of risk factors for phenotypically specific birth defects generally lack sufficient numbers of subjects except for highly prevalent exposures, leaving case–control studies as the preferred design for risk factor discovery and confirmation [12]. Thus, several large-scale case–control studies have been launched, employing rigorous diagnostic criteria and specific outcome definitions [12–15].

Despite the operational efficiency of case–control studies, exposure measurement remains a challenge because it often relies on maternal recall, and biomarkers or standardized documentation of exposures are not routine for requisite cohorts of hundreds of thousands of newly pregnant women. The difficulty of accurate retrospective exposure measurement is exacerbated by the relatively short period of organogenesis necessitating recall of episodic exposures at the level of day or week. A greater appreciation for fetal development has spurred epidemiologists to collect more precise data on the timing of gestation and exposures, thus reducing exposure misclassification and improving the sensitivity of risk estimation. Tools, such as calendars and picture books, have also been developed to aid recall [16, 17].

Along with improvements at the data collection level, investigators now have a better understanding of causal models and estimate risks without erroneous adjustment for known collider or intermediate variables [18]. For example, women who take periconceptional folic acid supplements are more likely to undergo prenatal diagnostic testing, but prenatal diagnostic testing is not a confounder of the association between folic acid exposure and neural tube defect outcome and attempts to adjust for its effects can produce bias. Also, many exposures are shared risk factors for both birth weight and birth defects. However, because birth weight is not an antecedent to exposure, it cannot confound birth defect associations, and therefore, attempting to adjust for birth weight can produce biased results [19].

This boom of epidemiologic studies and employment of improved methods has produced myriad exposure birth defect associations, but the list of consistent, robust, biologically plausible causal or risk factors is relatively short [20]. Thalidomide, folic acid deficiency, isotretinoin, valproate, carbamazepine, cigarette smoking, high-dose alcohol, diabetes, and assisted reproductive technologies can all be considered *causal* factors based on the strength of evidence, which includes multiple large-scale studies, detailed outcome definitions, consideration of gestational and exposure timing, and/or appropriate causal modeling. On the other hand, selective serotonin inhibitors, corticosteroids, proton pump inhibitors, opioids, aspirin, common cold, zinc, cocaine, caffeine and low-dose alcohol can only be considered *risk* factors with weaker evidence due to inconsistent results, sparse data, and/or absent biologic plausibility.

As epidemiologists chip away at the discovery of causal factors for birth defects, the larger body of findings that are either null, weak, or contradictory offers an important clue: Pathogenesis is quite complex. To understand normal and abnormal embryologic development, metabolomic, proteomic, genomic, and epigenetic studies are necessary. The tools to explore these -omics are developing rapidly, but in the case of birth defects, the timing of organogenesis limits access to biomarkers in the early embryonic period.

The appeal of understanding pathogenesis for primary prevention is a noble goal, but acknowledgement of inherent methodologic barriers that contribute to relatively slow progress leads to the question: Where does birth defects epidemiology sit in the "consequentialist epidemiology" paradigm for which the central concern is improving health outcomes? If primary prevention through understanding pathogenesis and etiology is not readily achievable, what directions might the field take with more achievable improvements in health outcomes?

Future Directions

Consider health-care assessment. When a baby is born with a congenital anomaly, the immediate short-term and long-term health-care needs vary substantially depending on the phenotype and family choices. Important questions would be whether every family has access to high standards of care, and if not, what barriers are there and what interventions can be implemented to eliminate barriers. Given the rarity of specific birth defects, optimal care may require highly specialized services that are available only in selected cities. Prenatal diagnosis should provide lead time to find such services, but barriers to accessing either prenatal diagnostic testing or specialized

services are likely, particularly for the latter. An example of this is fetal surgical repair of open spina bifida, a procedure with clear evidence of success on neurological outcomes [21]. However, to benefit from this procedure, the mother and fetus must have early and accurate prenatal ultrasonography, counselling on treatment options and risks, access to one of the few experienced treatment centers, and personal and insurance resources to cover the substantial costs. A less dramatic example is treatment for clubfoot, with serial casting, prostheses, and/or surgery [22]. Specialty services are more widely available but still require an affected family to travel to a major metropolitan area for fitting, follow-up care, and, if necessary, surgery. These scenarios are envisioned in developed countries with higher standards of care. It is important to recognize the enormous need for studies on optimal delivery of high-level care in less developed regions of the world. A study of low and middle income countries found that 67 % of deaths associated with oral clefts, heart defects, and neural tube defects could be prevented, and associated disease burden could be reduced by 57 % if improvements in surgical programs and other services were implemented [23••].

Much clinical research has addressed questions of the most effective treatments for many birth defects. However, follow-up may be limited to short-term outcomes based on clinical management. For treatments aimed at improving functional outcomes, such as respiration, nutrition, hearing, or mobility, studies of short-term outcomes are appropriate and essential to identify best treatments. However, treatments with longstanding improvements in both functional outcomes and quality of life are most desirable and worthy of study. Indeed, such research would optimally evaluate comprehensive care in which all needs are considered, including corrective surgery, physical and occupational therapy, family counselling, and both physical and mental health-related quality of life. This last outcome deserves special attention because it should supersede all others. In other words, an individual might determine that treatment lowers their quality of life. An acquaintance of mine with hemifacial microsomia serves as an example; he elected to forego corrective cosmetic surgery as a teen because it would have involved lengthy hospital stays and would have interfered with his quality of life. It is worth noting that research questions related to functional outcomes and quality of life pair with those related to access to care, as discussed above. Overall, the outcomes of greatest impact should be those that lead to a happy and satisfied childhood and adulthood. However, many studies of long-term outcomes in children born with specific birth defects are qualitative in nature or include only a series of cases [24–26]. Cates states in his commentary on consequential epidemiology [2••], "we intuitively think in terms of both numerators and denominators unlike our sister disciplines in the health field who are more numerator-prone." Thus, understanding and improving the sequelae of specific birth defect phenotypes is a field that is wide open for the epidemiologist's expertise.

While the above scenarios on health-care assessment represent a major shift of emphasis for the many birth defect epidemiologists with a risk factor focus, some relatively minor shifts to etiologic research would also be compatible with the consequentialist agenda. Specifically, research questions can be sharpened toward translatable results. For example, a recent simulation study estimated the potential impact of fortifying corn masa with folic acid on neural tube defect outcomes because folic acid intake is lower in Latina populations [27]. Comparative effectiveness studies of treatments with known or suspected birth defect risk profiles also offer the potential for important, translatable results. For example, several anti-epileptic medications have been linked to specific birth defects [28]. Studies aimed at comparing specific agent's anti-seizure effectiveness and birth defect risks would inform clinicians and patients about the risks and benefits of treatment options [29]. As the size of data resources on risk factors and birth defects have grown in recent years, studies that target factors that modify the impact of known risk factors can be helpful in refining public health messages. For example, in the National Birth Defects Prevention Study, increased risks of specific birth defects associated with maternal use of nitrosatable drugs were ameliorated among women with high vitamin C intake, a known nitrosation inhibitor [30]. Mediation analyses offer another opportunity for translatable results while exploiting existing data resources. A recent study of assisted reproductive technologies and NTDs serves as an example in which nearly all of an approximate doubling in risk was mediated through multiple gestations, suggesting that risk may decline if fewer embryos are transferred [31].

To stay within the existing framework of identifying risk factors for birth defects, a consequentialist epidemiologist would consider the impact of potential future interventions on the outcome. Factors for which there are existing health advisories would be of less interest. For example, regardless of whether high-dose alcohol intake, cigarette smoking, or obesity cause specific birth defects, major public health efforts are already in place, including strategies for prevention, reduction, or cessation strategies. On the other hand, infections are amenable to intervention and should be evaluated as potential risk factors for birth defects. Indeed, the major impact of some infections, e.g., Rubella and cytomegalovirus, is on the organogenesis [32, 33]. In the case of Rubella, vaccination in early childhood is recommended to avoid primary infection in pregnant women and subsequent birth defects in offspring. However, most infectious agents have been understudied as causal factors for birth defects. While epidemiologic studies would optimally include serial measures of biomarkers of specific microbial agents, such studies would be difficult to implement. Routine collection and storage of early gestation maternal serum samples across diverse

pregnant populations are essential to serve as a resource for examining infectious risk factors for rare birth defects to move toward intervention strategies. From a consequentialist viewpoint, continued surveillance of potential birth defects risks is warranted for new exposures, particularly medications. For example, new anti-obesity products are emerging on the market, some of which contain agents suspected of teratogenesis [34]. However, unless such exposures are common or their teratogenic effects are quite large, the impact of identifying associations and subsequent interventions would likely result in only minor reductions of specific birth defect occurrences. Nevertheless, it is imperative that potential teratogenic risks are evaluated to inform clinical decision-making.

Conclusion

In conclusion, etiologic studies of specific birth defects play an important role, but epidemiologists could significantly increase their impact on public health by extending their research endeavors to address barriers to optimal outcomes among those affected with birth defects. Such research should involve cross-disciplinary teams, including epidemiologists, health economists, policy analysts, social psychologists, clinicians (e.g., physicians, nurses, and occupational therapists), clinical care coordinators, and interventionists. Though changes in research agendas and establishing new collaborations are not easy for epidemiologists to accomplish, identifying the etiologies of specific birth defects has proven to be enormously difficult to achieve as well. Galea and Cates' call for consequentialist epidemiology [1, 2] rings true in the field of birth defects research and deserves action.

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Compliance with Ethics Guidelines

Conflict of Interest MM Werler declares no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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