

Human Embryonic and Fetal Death

Edited by

Ian H. Porter

Ernest B. Hook

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*Birth Defects Institute
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This volume is dedicated to Ellen J. Heenehan . Mrs. Heenehan prepared and edited camera ready copy for publication of all the proceedings of the symposia of this series since their inception in 1970, when she joined the Birth Defects Institute. She died on June 25, 1980 shortly after she completed her work on this volume.

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PREFACE

This volume is based upon the proceedings of the 10th Annual Birth Defects Institute Symposium held in Albany, New York, on October 29 and 30, 1979.

At the time we planned this symposium we were struck by how little systematic data were available on human embryonic and fetal death and by how scattered they were in diverse sources.

In one sense, of course, a large fraction of publications in obstetrics deal, at least indirectly, with the prevention of human embryonic and fetal death, but this literature is concerned primarily with the clinical management of pregnancy. To our knowledge, there is no previous volume, nor even an extensive review article, exclusively devoted to descriptive and analytical studies of human embryonic and fetal deaths. We were fortunate in being able to find a number of eminent teratologists, epidemiologists, geneticists, and clinicians who could not only review the critically available literature but who could also present their recent research findings published here for the first time. We hope the proceedings of this Symposium will serve both as a useful initial reference source and as a guide to further investigation by the increasing number of scientists and public health workers interested in biological and epidemiological investigations of human fetal and embryonic death.

It is, of course, not always possible to cover every facet of a field in a series of edited articles, nor can every article review a particular field comprehensively. We have, therefore, attempted in the first chapter of this volume to address briefly some issues, or at least provide references for topics not extensively considered elsewhere, and to emphasize some methodological and terminological considerations that may not be evident immediately to those not working in the field. Many of the problems that make investigations of prenatal mortality difficult are not obvious to those who work only with aspects of postnatal morbidity and mortality. While the nature of such difficulties is, at the least, implicit in most of the articles presented here, we believe it worthwhile also to state them explicitly in this introductory chapter.

Lastly, we acknowledge with gratitude the efforts of the many colleagues who contributed to the smooth running of the Symposium and to the production of these proceedings. These include, in particular, Luba Goldin, our administrative assistant; Kathy Miller, Veronica Motts, Cathy Ruth and many other members of the Birth Defects Institute. We are also grateful to Drs. David Axelrod, the

Commissioner of Health, Glenn Haughie, Director of Public Health and Robert Huffaker, the then Acting Director of the Division of Laboratories and Research, for encouragement and support.

Ian H. Porter
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TERMINOLOGICAL CONVENTIONS, METHODOLOGICAL CONSIDERATIONS, TEMPORAL TRENDS, SPECIFIC GENES, ENVIRONMENTAL HAZARDS, AND SOME OTHER FACTORS PERTAINING TO EMBRYONIC AND FETAL DEATH

Ernest B. Hook

Ian H. Porter

This chapter deals with some themes and lists some references not considered elsewhere in this volume.

The sections of this chapter relate to the following factors.

- Terminology
- Methodology
- Temporal trends
- Specific gene effects
- Paternal age
- Multiple births
- Infectious agents
- Environmental hazards and drugs

This is not a definitive discussion of these subjects as they relate to the study of human embryonic and fetal death, but rather an introduction which, with the references, will, we hope, be helpful to the interested reader.

TERMINOLOGICAL CONVENTIONS

Human embryonic and fetal death is an unwieldy term for what many clinicians refer to as "reproductive loss" or "reproductive wastage". Unfortunately, "reproductive loss" is an ambiguous term which may be confused with the loss of reproduction associated with many factors, *e.g.*, menopause or surgical procedures. And "reproductive wastage" may also imply something quite different than embryonic and fetal death, *e.g.*, some types of contraception.

Unfortunately, there is no single term which applies to "intracorporeal" death of the conceptus after the start of gestation.* "Embryonic" death in

*We use "intracorporeal" rather than "intrauterine" because death of the conceptus may occur in the fallopian tubes or vagina. "Prenatal mortality" is perhaps a term which comes closest to our intended meaning, but might be misunderstood as applying to maternal death.

humans usually refers to death during the first eight weeks of "intracorporeal" existence, *i.e.*, ten weeks from the date of the last menstrual period; "fetal" death applies to subsequent mortality, although some statisticians use "fetal" death to include embryonic death.¹ The term "abortion" not only has a range of meanings in the medical context but a different meaning legally and to the lay reader. In the British Medical Dictionary,² "abortion" is defined as "expulsion of the fetus before the beginning of the 28th week of pregnancy", and to the "actual product of an abortion". It is of interest that there is no qualification as to the viability of the fetus.

Presumably, a livebirth before the 28th week would also be an "abortion" under this definition. But to the lay and legal mind an "abortion", of course, usually means an induced event, and "miscarriage" has been the term for the usual medical meaning of "abortion".

Until recently, the term "stillbirth" explicitly applied to fetal *deaths* that occurred subsequent to the 28th week.² But because of the increasing viability of products of gestation under 28 weeks, the demarcation point between abortion and stillbirth has been changed in many jurisdictions in the U.S. to 20 weeks.¹ (But, in some jurisdictions at least until recently, "stillbirth" was used for *all* fetal deaths.) To confuse matters even more, because of the difficulty in gauging the gestation accurately, the World Health Organization (WHO) has recently recommended that the abortion-stillbirth distinction be made on the basis of birth weight, not gestation length.³ For purposes of *international comparisons* they suggest the term "stillbirth" be applied only to infants weighing 1,000 gm or more. Dead fetuses weighing more than 500 are also to be termed "stillbirths" but not used in international comparisons. "Abortion", they indicate, should apply to expulsion or extraction of a fetus or embryo weighing 500 gm or less (approximately equal to 20 to 22 completed weeks of gestation) "or an otherwise product of gestation of *any* weight and specifically designated (*e.g.*, hydatiform mole) irrespective of gestational age and *whether or not there is evidence of life...*"³ (Emphasis added.) The intent is not precisely clear, but apparently a fetus weighing 500 gm or less born alive is still counted as an "abortion" under this definition. Note moreover, that diminished birth weight associated with multiple births is not adjusted for. This is unfortunate because a twin of low birth weight at time of delivery has a lower risk of being "stillborn" than a singleton of same birth weight, because the twin is usually more "mature" in terms of gestational length.⁴

While some clear operational definition is needed for interjurisdictional comparisons, giving new meanings to old terms only spreads confusion in the vain attempt to achieve greater accuracy. A less euphonious but more precise term for what the WHO terms an "abortion" might simply be "very small fetus".

Semantic decisions occasionally impose an unintended conceptual burden and may result not only in confusion but in statistical artifacts. It took a long

period before the term "premature" was distinguished from "low birth weight", and the concepts of intrauterine growth retardation and dysmaturity were recognized. The WHO recommended nomenclature represents a semantic regression. If methodological equivalence for international comparisons is to be sought, an unambiguous term without some other traditional usage should be employed.

In this volume we have not attempted to enforce terminological exactitude, not least because we have no single simple term to enforce. The meaning of the terms employed thus may vary somewhat in the usage of various authors. In the chapters to follow, "abortions" may be much later and heavier than WHO or the National Center of Health Statistics would like, and "fetal deaths" may occur at gestational stages when anatomists would be referring to "embryonic deaths". Despite our editorial role, we remain unrepentant and advise the reader to seek meaning in the context.

There is another terminological difficulty which is potentially even more confusing. Gestational length is almost always timed by the clinician and the epidemiologist as beginning at the first day of the last menstrual period (LMP) before pregnancy. Under this definition, the normal gestational period is 280 days. This is, of course, a convenient operational definition, but it is biologically incorrect. Thus, embryologists and anatomists who study early stages of human pregnancy time events from the presumed start of conception, which is usually but not always 14 days after the first day of the LMP. For them human gestation is normally 267 days. (See, for example, reference 5.) This convention is more correct biologically but less frequently used in the literature. Thus, the "first four weeks" of gestation when used by epidemiologists (but not embryologists) usually refers to the first two weeks of life of the conceptus.

This terminological ambiguity, unlike that described above, can not always be resolved from the context of the discussion, and some caution is urged whenever the definition of gestation length is not explicitly given. Difficulties in unambiguously denoting the length of gestation also vex the experimental scientists, so that, for example, a day 10 embryo may be almost one day older than "an embryo of the 10th day". For further discussion of this issue — which is of some importance in teratological studies — see reference 6.

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METHODOLOGICAL COMPLEXITIES IN EVALUATING EMBRYONIC AND FETAL DEATH

The great difficulty in methodological investigation of embryonic and fetal deaths has frequently been unappreciated by those seeking to link putative environmental hazards to such outcomes. The difficulty documenting the occurrence of death, particularly embryonic death, the problems of selective recall in those having adverse outcomes of pregnancy compared to those with normal outcome, and the likelihood that pregnancy complications associated with embryonic or fetal death lead to earlier referral for medical care make systematic epidemiological investigation extremely difficult. It is worth emphasizing again some of the specific difficulties. Early embryonic or fetal death may be overlooked as a skipped or a delayed menstrual period. The event may occur before the woman has suspected her pregnancy or had confirmatory diagnosis. The recollection of such an event, or of a later fetal death, for that matter, may be biased in that a woman may be more likely to recall such an episode (or perhaps more likely to interpret a delayed period as an embryonic death) if she knows she has been exposed to some putative embryotoxin, especially one which has received a good deal of publicity. Conversely, a woman who has experienced a documented spontaneous embryonic or fetal death may be more likely to recall prior events than one who has not. And lastly, women with a "normal" course of pregnancy may come to medical attention later in gestation than those who have "threatened abortions" or other complications. Thus, identification of good "controls" or obtaining useful data on comparison populations may be very difficult. These points are in one sense elementary, but are often ignored by those whose analytic experience is primarily with other types of morbidity and mortality. All of these difficulties are addressed in this volume by contributors who have struggled with these issues in attempts to make reasonable inferences from available data. Even the simple measurement of the rate of embryonic and fetal death in the population is subject to question because of these methodological problems. (In addition to the references cited by Harlap in this volume, see also the work of Abramson.^{1,2}) It appears that at least one past source of confusion, the report of abortions as "spontaneous" which were directly or indirectly "induced" in some manner, is no longer as great a confounding

problem in the U.S.A. because legal changes have removed the impetus to conceal such events. Nevertheless, for the reasons noted above, embryonic and early fetal deaths are among the most difficult of any adverse human outcomes to investigate epidemiologically.

Lastly, there is a theoretical problem in study of putative causes of embryonic and fetal deaths which may be almost impossible to eliminate. Even apparent associations that are statistically valid may be hard to explain straightforwardly, as it is always conceivable that some factor that appears to be associated positively with embryonic and fetal death is rather fetoprotective, and acts by postponing the time of death from an earlier stage of gestation when such an event would be less likely to be recognized, to a later stage. Such a theoretical caveat is almost impossible to exclude. In this respect, of course, the argument resembles the *ad hoc* legal defense of the makers of thalidomide who suggested that perhaps this drug was not inducing birth defects but rather allowing affected embryos (who would, it was claimed, otherwise spontaneously abort) to survive to livebirth. This argument at least could be rendered implausible by the fact that the specific defects observed correlated closely with the gestational time that exposure to the drug occurred, in agreement with the concept of the "critical period" established in experimental teratology. But for embryonic and fetal deaths, evidence of this type is very hard to come by, and it may be in fact impossible to distinguish, at least by "retrospective" studies, whether an agent or biological factor is associated with diagnosed embryonic and/or fetal death because it tends to delay the event to a time when recognition is more likely or because it is actually embryotoxic.

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RECENT TEMPORAL TRENDS IN FETAL DEATHS

A notable drop in reported (spontaneous) fetal death rates has occurred in the past 15 years. Evidence of this trend in Upstate New York appears in Tables 1, 2, and 3 for deaths at or after the 20th or 28th week of gestation. We emphasize we exclude induced pregnancy terminations in calculations of these rates.

Table 1 represents crude and standardized rates of fetal deaths in White pregnancies, which constitute about 90% of those in this jurisdiction. At the time we prepared this report we did not have data specifically on the Black pregnancies throughout this interval that could be standardized in this way.