Special Article

The Pathologist and Perinatal Medicine
Part I - Perinatal Epidemiology - Improving the Data Set

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Introduction

The perinatal pathologist can, as an integral part of the maternal-fetal medicine team, make a number of important contributions to this rapidly developing, stimulating and challenging field of clinical medicine. These include: -

1. At individual case level, providing diagnostic information to aid in planning the management of subsequent pregnancies at risk.
2. At hospital, regional and national level, improving the accuracy and validity of perinatal epidemiological data, and thereby contributing both to better surveillance of patterns of perinatal disease and to the overall planning of health care services.
3. At an individual case level, at unit level and on a regional basis, playing a key role in the quality assurance and auditing of new technologies, particularly those used in prenatal diagnosis, fetal therapy and neonatal intensive care.
4. Through liaison with colleagues in clinical pathology, encouraging the development of diagnostic laboratory services, technology essential, appropriate for supporting perinatal medicine and the effective use of expensive or scarce manpower and material resources.
5. By careful and thoughtful examination and evaluation of the individual fetus and placenta through collaborative and interdisciplinary studies contribute to the further understanding of developmental biology and of the pathogenesis and evolution of disease in the fetus and newborn.
6. In countries where there is an increasing tendency to litigation in obstetrics, provide an impartial opinion and act as an expert witness.
7. Provide an educational model to enhance the status of the autopsy as a central pillar of quality assurance and audit in clinical practice.

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Many of these functions revolve around the perinatal autopsy.[1] It is however obvious that full and detailed perinatal autopsy though highly desirable, may not always be possible or appropriate and that some of these objectives can be fulfilled without complete autopsy.

There are in addition several secondary roles for the pathologist in perinatal medicine. He or she should take responsibility for ensuring that even if no autopsy has been carried out, there is dignified and appropriate handling of the dead fetus or newborn in the hospital mortuary or histopathology department, that viewing of the baby is encouraged and that burial arrangements are not impeded in any way. Several techniques for rapid and cosmetically acceptable reconstruction of small fetal bodies after pathological examination are available and further contribute to improving the management of perinatal death. The pathologist may further contribute directly to the clinical management of perinatal bereavement by ensuring that fetal and neonatal mementoes such as pho tographs, footprints or locks of hair are collected and offered to the parents of the infant. The demand for this type of service varies among cultural, ethnic, religious and socioeconomic groups and is also influenced by the personal attitudes of the parents, the gestational age of the fetus, age and parity of the mother.[2] The perinatal pathologist may also become directly involved with counselling parents after a stillbirth or neonatal death[3]; again this is highly dependent on local resources and attitudes.

The Pathologist and Perinatal Epidemiology

The purpose of collecting any epidemiological data can be summarised as a process firstly of identifying a problem, then developing policy, strategy and options for action, implementing policy and finally evaluating outcomes. This is no less valid in perinatal epidemiology than in other areas of disease prevention. This paper, which is the first of two addressing the broader role of the pathologist in improving perinatal care and in advancing knowledge of the aetiology, pathogenesis and outcome of disease in the fetus and newborn, explores the contribution of the pathologist to improving the quality of perinatal epidemiological data. This aspect has been chosen in order to emphasise the value of quality epidemiological data for planning perinatal health services and for determining priorities for resource allocation, not only to tertiary level units but also at primary health care level to enable preventative strategies to be developed.[4] While the emphasis is on perinatal mortality data and its appropriate classification, other aspects of perinatal epidemiology will also be briefly discussed.

Regardless of whether data is intended to be used for planning health services or for comparison

between population, the validity and potential utility of perinatal statistical data, especially data related to mortality and to congenital malformations, is heavily dependent on the accuracy of recording of the original information and on the consistency of case definition .

There is a wide range of perinatal epidemiological data which the pathologist can influence positively or by omission and error render less valid (Table I).

Perinatal Mortality Data

Improving Quality and Utility

Perinatal mortality rate has long been used by clinicians, sociologists and politicians as an indicator of the quality and utilization of medical services in general, and for comparisons between various geographically, demographically and socio-economically defined population. While it has been lucidly argued that the perinatal mortality rate is no longer a useful or appropriate indicator of perinatal health[5], alternative indicators such as morbidity rates which may eventually prove to be more valid are much more difficult to define. As a crude indicator of overall level of medical care perinatal mortality rate is an easily definable parameter and has at least the advantage of being able to show changes over relatively short periods of time.

The reasons for collecting perinatal or any other mortality data are fairly obvious and include:

1. Monitoring longitudinal trends in overall rates.
2. Recording changes in the pattern and incidence of various causes of death.
3. Defining differences between disadvantaged and comparatively advantaged groups in a population.
4. Providing a basis for comparision between health care units and regions.
5. Providing a basis for confidential enquiries in a unit or region.

One of the original reasons for perinatal mortality surveys was to

Table 1 ***The Pathologist's Contribution to Perinatal Epidemiology***

Improving

- quality and utility of perinatal mortality data.
- quality and utility of maternal mortality data.
- ascertainment of chromosomal abnormalities and of congenital malformations.
- validity of twin studies.
- diagnosis and investigation of congenital and perinatal infections.
- surveillance of adverse outcome of high technology fetal and neonatal diagnosis and intervention.
- ascertainment of Sudden Infant Death Syndrome and other causes of sudden unexpected death in the neonatal period.
- information on outcome of randomised controlled clinical trials with high mortality.

allow confidential enquiry into individual perinatal deaths including assessment of avoidable and unavoidable factors. Now there has for sometimes[6], however, been a trend away from this approach to perinatal deaths. It is now much more common to evaluate patterns of perinatal death in such a way that attention is focused on specific areas of deficiency in perinatal care which seems to be more useful approach. Confidential enquiry is, however, still carried out on individual maternal deaths where the numbers are much smaller and preventable factors often much more clearly defined. Even though still generally accepted as a measure, however, crude of the effectiveness of health care, perinatal mortality rate alone is of limited value without cause specific information. Some process of classification is therefore required in order to identify specific issues and problems which permit specific recommendations for change.

Classification of Perinatal Mortality Data

Classification has been and continue to be a problem, in part because of the complex clinical situations which surround most perinatal deaths. It remains difficult to achieve agreement between obstetricians, neonatologists, pathologists and epidemiologists on the best classification system to use at hospital and local area level and even more difficult at national level. Any candidate classification system needs to be one which is designed to make use of data that is reasonably likely to be available or obtainable, and in such a form that subsequent data analysis can address those questions most likely to be asked by clinicians, regional health administrators, sociologists and politicians. Some of the requirements for a useful classification system are outlined in Table 2. It is only worth classifying perinatal mortality data if the results of the process lead to identification of deficiencies in perinatal care and of strategies for improvement. It is practical and logical therefore to approach perinatal death classification at several levels, depending on the available resources and the achievable outcomes.

The most obvious and primary distinction is between stillbirth (late fetal death) and neonatal death and

Table 2 *Design Criteria for a Classification System for Perinatal Death*

- Uses data that is easily available or obtainable.
- Uses a format that allows important perinatal issues to be addressed retrospectively.
- Has a small number of mutually exclusive categories.
- Is simple to use and able to be validated.
- Is not dependant on full and specialised autopsy.
- Allows second tier subclassifications to meet local needs.

difficulties in definition may arise even at this level. Nevertheless, the simple process of distinguishing between stillborn and liveborn infants at least enables two distinct groups of fundamental issues to be identified. Reduction in the stillbirth rate is, at least hypothetically, more likely to be achieved. 1. By primary strategies which target, by means of educational campaigns and antenatal screening programs, important maternal risk factors such as nutritional deficiencies, infections, chronic diseases, drug abuse and smoking, 2. By secondary strategies such as those aimed at improving access to antenatal care and thus enabling early detection and treatment of those maternal conditions that present defined risks to the fetus.

Reduction of the neonatal mortality rate depends not only on the availability of facilities and technology for neonatal intensive care but also, and perhaps more importantly in the developing world, on basic preventative health strategies to reduce the neonatal mortality from preventable causes such as birth asphyxia, infections, neonatal tetanus or hypothermia. Moreover, any strategy aimed at lowering the incidence of preterm birth such as those associated with eradicating those vaginal pathogens known to induce preterm labour[7] is also expected to lower the neonatal mortality and morbidity rate.

Reductions in the perinatal mortality rate in some categories of disease such as congenital malformations may, however, be misleading. Serum screening and ultrasound programmes to detect neural tube defects early in the second trimester, with subsequent termination of pregnancy, have resulted, not in a decrease in overall prevalence but merely in a shift in the numbers of deaths attributable to these malformations into the preregistrable age group where they no longer contribute to perinatal mortality figures.[8]

If strategies to reduce perinatal mortality are to be effective then classification by birth weight or birthweight/gestational age combination is also essential since, there is an inverse relationship between perinatal mortality rate and gestational age/birthweight.[9] It is, however, fairly obvious that simple separation into numbers of live births and numbers of stillbirths in each birthweight grouping will still not be sufficient to define problems in delivery of perinatal services.

Over the past 25 years, as perinatal epidemiology emerged as a subspecialty area it became clear that there was a need for cause-specific classification; numerous attempts were made with visible contributions from pathologists. Perinatal death classification by primary post mortem finding was first used in a large scale survey in Britain in 1958 and again in the early 1970s.[10] Retrospective assessment of these surveys clearly demonstrates the difficulties that arise in attempting to assign a primary cause of death particularly when there have been several interacting obstetric and neonatal factors as there are in a high

proportion of perinatal deaths. In a later modification([11]) of this essentially pathologically oriented approach it was pointed out that with the sophisticated imaging procedures and other diagnostic techniques available, a high degree of accuracy of pathological diagnosis was obtainable even without autopsy. The US Collaborative Perinatal Project[12] used a custom-designed classification based exclusively on placental and fetal pathological findings but had the intrinsic disadvantage of depending on full autopsy by specialist perinatal pathologists. Two studies from Finland[13,14] also rely on detailed pathological examination. None of these classifications are particularly helpful as some are cluttered with unhelpful and inappropriate diagnoses such as placental insufficiency or diagnoses such as cord knots which is the cause of death and requires more rigorous pathological evaluation than was usually appreciated at that time. For a long time, the most workable classification of perinatal death was undoubtedly the so-called Aberdeen classification[15] with its emphasis on primary obstetric factors leading to stillbirth and neonatal death. This classification remained for many years the cornerstone of much perinatal epidemiology. It can, however, become quite difficult to ascertain which one of a number of high risk obstetric factors, such as maternal glucose intolerance or pregnancy induced hypertension, which may coexist in a pregnancy, should be regarded as the primary obstetric factor leading to poor outcome. Nor is it always clear in any particular case whether the cause of death should be attributed to the underlying obstetric disease, for example, pregnancy induced hypertension, or to a superimposed acute obstetric event such as major abruption. The successor to the Aberdeen classification, devised by Whitfield[16] is now widely used as a substitute but suffers some of the same problems as its predecessor because of the need for hierarchical decision making.

It was in 1980 that a perinatal pathologist[17] devised what is now widely regarded as the best and simplest system, a two-tier classification based on birth-rate-specific groups and five mutually exclusive pathologically-based categories of disease. What is now universally referred to as the Wigglesworth classification was, as its designer has since pointed out[9] never intended as a classification but merely as a way of approaching the investigation of perinatal death. It is applicable to all perinatal deaths whether or not autopsy has been carried out. It is by far the most useful primary classification of perinatal death for individual hospital, local area or regional studies; it has not yet anywhere been rigorously tested at a national level. It is paradoxically the essential simplicity of the system that has been criticised by obstetricians and paediatricians in tertiary level centres who claim that it does not provide enough clinical detail to be

useful. This criticism can be easily addressed in these centres by the development, to suit local needs, of detailed subclassifications to enable identification of more specific obstetric or neonatal factors or, if obstetric factors only are required, the secondary use of a modified Aberdeen classification. The Wigglesworth system has been subject to one major validation study[18] and has, as a result, been slightly modified and it is this modification which will be used here to illustrate an effective way of classifying perinatal deaths. It is useful in areas where the autopsy rate is unavoidably low, either because there are too few pathologists to carry out perinatal autopsies or where cultural and religious attitudes discourage or forbid the practice, and yet where data of a type more specific than that derived from crude perinatal mortality rates alone is required to help with planning health care services. In addition to being widely accepted in Europe, it has been effectively used in a number of areas of the developing world[19,20] most notably in a major study in Jamaica[21] which remains a useful bench-mark for regional perinatal mortality surveys. It is of interest that this work[22] showed that during the period of the study when, for local reasons the autopsy rate was high, there were, in comparison to the period in which the rate was low, only minor changes in the percentage of deaths assigned to the various categories, most notably and predictably in the category of unexplained antepartum death and in category 5 (specific causes).

Clinicopathological Approach to Perinatal Mortality Classification

The Wigglesworth classification and its modification[18] have five mutually exclusive categories:

1. Antepartum fetal deaths - macerated stillborn infants in whom death is assumed to have occurred prior to the onset of labour unless there is clinical evidence to the contrary
2. Major malformations that would be likely to have resulted in death or multiple minor malformations, whether or not they suggest a specific syndrome.
3. Conditions associated with immaturity - liveborn infants weighing between 1500 and 2499 g and surviving the first day of life, and all liveborn infants weighing less than 1500 g provided groups 2 and 5 are not satisfied.
4. All fresh stillbirths, macerated stillbirths in which there was evidence that death occurred during labour, all liveborn infants weighing between 1500 and 2499 g dying on the first day of life, and all normally formed live-births of 2500 g and above provided group 5 is not satisfied.
5. Those infants with specific causes of death such as red cell isoimmunisation, fetomaternal haemorrhage or congenital infection.

These groups can form the

basis of a satisfactory primary level perinatal death categorisation and can be achieved even if no autopsy has been performed. If consent for autopsy is denied, or not sought, or if no pathologist is available then, a basic examination of the stillborn fetus or dead neonate can be carried out by obstetric or paediatric medical staff. Relevant investigations can be initiated on maternal blood, cord blood and placenta and classification categories then assigned. By using the simple sorting process outlined below, (Fig 1.) useful epidemiological data may be obtained even when there are insufficient human or financial resources to allow perinatal autopsy or where health care priorities dictate that resources be channelled elsewhere. Such an approach could, if carried out systematically in the delivery room, nursery, autopsy room, or pathology department, laboratory and the results recorded on a simple data sheet, suitable for future analysis, form the basis of an efficient and functional means of perinatal death classification with minimal effort. It should be recognised that without autopsies the proportion of cases in category 5 will be underrepresented.

Sorting Process for Investigation of Perinatal Death

The investigation of perinatal death may be seen as a stratified process of increasing levels of complexity depending both on local resources, on community, parental religious and cultural attitudes. Investigation at the first level can be carried out even if

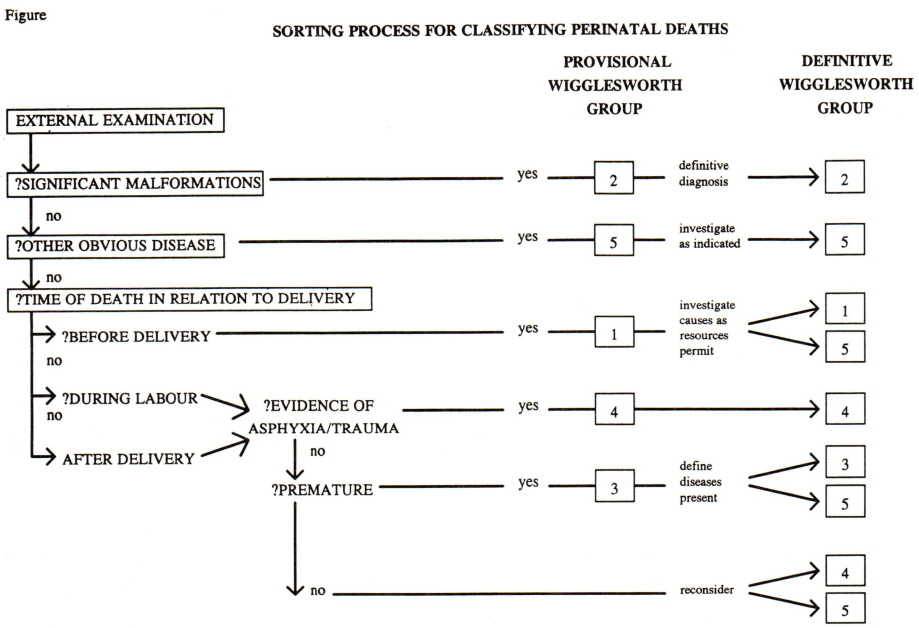

Figure 1. ***Sorting Process for Classifying Perinatal Death***

no pathologist is available since the basic examination can be carried out by the obstetrician or in the case of neonatal death by the neonatal paediatrician. The baby should be examined externally and any other accompanying diagnostic information such as ultrasound reports and neonatal x-rays reviewed to determine whether or not there are obvious malformations. Major malformations, whether single or multiple, place the baby in category 2. The findings of several minor malformations in a dead baby, even if these are not potentially lethal, should raise the possibility of a significant chromosomal abnormality and even if karyotyping cannot be carried out, also place the death provisionally in category 2. If significant malformations are absent then any other significant external abnormalities such as marked pallor, skin lesions such as petechiae or pustules, extensive haemorrhage or hydrops should be noted and accompanying clinical and laboratory data reviewed for evidence of specific disorders including red cell isoimmunisation and known or suspected congenital infections. If convincing evidence of a specific disease is found, then the death is provisionally classified into group 5. Suspected specific diseases can be further investigated using fetal, placental or maternal specimens; the extent of investigation depends on the resources available and the degree of detail demanded.

If there are no lethal congenital malformations or reason to suspect a chromosomal abnormality and no obvious signs of any specific disease then, for a stillborn fetus, the next stage is to decide whether, on the basis of its macroscopic appearance and using any clinical data available, the death occurred before the onset of labour or during labour. Determining whether signs of maceration are present is easy though attempting precise assessment of the period of time between intrauterine death and delivery is unwise. A normally formed fetus who convincingly shows no signs of maceration should be regarded as an intrapartum death unless there is cardiotocographic or other evidence to the contrary, and, unless there is also suspicion of a specific disease, should be classified into group 4 (asphyxial deaths in labour). The question of whether or not placental abruption is the underlying cause of an asphyxial type of death can usually be easily resolved and this provides an optional but important sub-category of asphyxial deaths (4b), to distinguish these cases from those in which asphyxia is related to the process of labour and delivery (4a). Known or suspected intrapartum deaths where no autopsy is to be carried out require careful external clinical and often radiological examination in order to identify clearly whether there is evidence of birth trauma. Cases with obvious major birth trauma are placed in group 4a along with birth asphyxia. Overwhel-ming fetal sepsis, such as that caused by group B Streptococcus,

and the acute fetal anaemia with hypovolaemic shock which may result from massive fetomaternal haemorrhage or a ruptured fetal vessel, may present an unexpected intrapartum death. These causes of death are relatively easily diagnosed with appropriate laboratory investigations but without necessarily needing an autopsy.

Group 1, the normally formed fetus dying before the onset of labour without obvious specific disease, is a large category which, depending on clinical and epidemiological resources available may then be sub-classified according to associated maternal, fetal and placental risk factors including pregnancy induced hypertension, maternal glucose intolerance and idiopathic intrauterine growth restriction. None of which are necessarily causes of death but factors predisposing to sudden death before labour. Truly unexplained antepartum death is a diagnosis of exclusion ideally requiring a very detailed autopsy protocol and extensive laboratory investigations analogous to that required for ascertaining the true incidence of Sudden Infant Death Syndrome and while highly desirable may be beyond the resources of many units.

Evaluation of neonatal deaths is again best approached by external examination of the baby and review of perinatal and postnatal records. If the baby is significantly premature and has lived for more than a few hours then autopsy is useful in order to evaluate the extent and severity of known prematurity related diseases such as hyaline membrane disease and its sequelae, pulmonary air leaks, periventricular haemorrhage, necrotizing enterocolitis and perinatally and postnatally acquired infection. It is particularly desirable that neonatal intensive care units, particularly those in the earlier stages of development, try to achieve a high autopsy rate in order to monitor the local incidence and pattern of iatrogenic disease and of complications of treatment. The term or near term baby born in apparently good condition, that who dies within the first few days of life also usually requires autopsy unless very obvious clinical factors have emerged. Specific conditions such as unsuspected congenital heart disease, overwhelming infection or metabolic disorders are not infrequently found, allowing classification of the death into category 5. If autopsy is not possible then it is again stressed that rigorous evaluation for preventable or treatable conditions such as birth trauma, severe anaemia and overwhelming infection is desirable.

The second level of investigation uses the same framework with some form of alternative, simplified or limited autopsy procedure. This can include radiographic examination[23], post-mortem ultrasound[24], limited dissection of for example chest, cranial cavity or abdomen, limited incisions through which most organs are examined or if the technology is available, ultrasound-guided or blind needle biopsy of organs. These proce-

dures may be useful when autopsy consent has been denied and resources are easily available for alternative investigations and when full autopsy is difficult because of a shortage of pathological expertise or enthusiasm.

The third level of investigation implies full autopsy examination by an experienced pathologist using standard techniques and with appropriately selected laboratory investigations; there is general agreement in the profession about quality standards at this level.[25-27] It should however be emphasised that an inadequately performed autopsy without appropriate tissue sampling and without understanding of the underlying clinical processes may be less helpful and more misleading than no autopsy at all. The general anatomical pathologist with no special knowledge is therefore strongly advised to consult an experienced perinatal pathologist and, in some circumstances, a paediatric radiologist, in any difficult case particularly where there is a suspected genetic basis to the disease, to avoid providing misleading information and thereby not only causing inaccurate prognostic information to be given to individual patients and subverting the clinical audit process but also contributing to distorting local epidemiological data.

When resources permit, especially, where there has been expensive and high technology fetal or neonatal diagnosis or intervention before death, a detailed autopsy is highly desirable. The value of the autopsy in this context will be the subject of a further paper.

Before leaving the subject of perinatal mortality classification the so called verbal autopsy should be briefly discussed. This is an epidemiological tool which has been widely used in some parts of the developing world, notably in rural Africa, to determine, by means of interviewing bereaved relatives, likely causes of death in adults and older children and has been recommended for use by the World Health Organisation as of use in assigning cause of death in trials of malaria control strategies. The uses and limitations of this method have recently been evaluated in a prospective study in Kenya.[28] It is difficult to see that such a method could ever have more than very limited use for providing cause specific perinatal mortality data except perhaps to identify very gross congenital anomalies and to crudely estimate the prevalence of deaths from certain conditions such as neonatal tetanus where the symptoms and signs may be well recognised by local population.

The usefulness of the Wigglesworth classification is that it highlights, at unit and regional level, deficiencies in perinatal services and thereby allows intervention strategies to be considered. A high incidence of deaths in group 1 may point to problems in access to or delivery of antenatal care. A high proportion in group 2 may indicate either a low uptake of antenatal screening for

malformations or, especially if occurring in a particular geographical area or occupational group, raise the possibility of environment teratogens. A high proportion of deaths in category 3 focuses attention on the adequacy of neonatal care, both primary health care, and availability of and access to neonatal intensive care services while in high proportion of cases in category 4 should direct attention to delivery room practices.

There remain major and well documented problems with the accuracy of perinatal mortality data, some of which are outside the sphere of influence of the pathologist. These include inconsistencies in defining and interpreting stillbirth versus early neonatal death, and failure to register deaths, particularly stillbirth and neonatal deaths of very low birth weight. In an elegant study in Belgium and the Netherlands, Kierse[29] highlighted the wide degree of personal variation in reporting deaths of very low birthweight babies; this variability can clearly have a major impact on the validity of perinatal mortality data. To this should be added the notorious inadequacy of the death certificate information often used for classifying causes of death when often inaccurate and based on poor quality information. All these problems apply in varying degrees to perinatal data collections at all levels ranging from national to local area to hospital-based data and can make both longitudinal and comparative studies difficult.

Maternal Mortality Data

In those countries where the maternal mortality rate remains very high, the solutions are clearly social and political not medical or as bluntly stated recently "educate or die".[30] It has, however, been noted[31] that in those developing countries where substantial advances have been made into reducing maternal mortality there is still a place for improvement in the quality of cause specific data and it is here that the pathologist can make an important contribution. In particular it is important that maternal deaths associated with abortions are not underreported, as is clearly the case in many countries.[32] The pathologist can try and ensure that if evidence of pregnancy or recent delivery is found at autopsy in any woman of reproductive age, it is clearly, unequivocally documented and moreover ensure that such deaths are reported to the appropriate hospital or local surveillance body. It is particularly important that any death in any woman in the reproductive age range, in particular any sudden and unexpected death, any death related to sepsis of unknown origin and any death from a medical condition known to be exacerbated by pregnancy be adequately investigated to ensure that a maternal death is not overlooked simply because it has taken place outside the context of clinical obstetrics. Although not always possible, it is highly desirable that autopsies be carried out on all maternal deaths and that these

Tble 3 *Improving ascertainment of congenital abnormalities*

- Recognising subtle markers of chromosomal syndromes in macerated and inexplicably growth retarded fetuses.
- Ensuring that karyotyping of malformed fetuses is carried out where indicated.
- Ensuring that descriptive reports and diagnoses are of adequate quality to permit accurate identification of congenital anomalies.

autopsies be performed by or under the direct supervision of a pathologist who not only has special interest and expertise in the subject but also has a sound understanding of clinical obstetrics. Unless unnatural causes of death are suspected, maternal deaths, regardless of, whether they fall under the jurisdiction of the coroner or medical examiner are better carried out not in the hectic atmosphere of a overcrowded forensic pathology service but in the more academic environment of a teaching hospital. These autopsies merit time and concentrated effort may yield much additional valuable information about the pathology of pregnancy.[33]

Data on Chromosomal Abnormalities and Congenital Malformations

There are, if resources permit and facilities for karyotyping are readily available, several ways in which the pathologist may improve ascertainment of chromosomal abnormalities and congenital anomalies in general. (Table 3)

The pathologist, or indeed any other person examining a dead baby, should remember the possibility of aneuploidy, particularly in macerated stillbirths who are small for gestation age and who have accompanying minor malformations. If this is recognised and if resources are available, then karyotyping can be carried out using fibroblasts cultured from placental tissue (particularly amnion) or pericardium. Significant chromosomal abnormalities are not infrequently found.[34] It is particularly important for the pathologist to be aware of this possibility in the macerated stillbirth as these babies rarely receive a formal clinical examination either from an obstetrician or neonatal paediatrician and therefore may be inappropriately classified as unexplained deaths.

It is, unless virtually unlimited resources are available, neither practical nor appropriate for either the pathologist or the obstetrician to demand, or even encourage, karyotyping of first trimester miscarriages or of morphologically normal second trimester fetuses. The general incidence of chromosomal abnormalities is well known from the large studies[35] and the recurrence risk of the same abnormality in future pregnancies usually low.

There is, however, a clear indication for karyotyping most obviously malformed fetuses, whether spontaneously aborted or electively aborted after prenatal diagnosis by

ultrasound, unless amniocentesis for karyotyping has already been performed, or the abnormality is an isolated neural tube defect. The finding of a major chromosomal abnormality associated with single or multiple malformation can make a major difference to the assessment of recurrence risk.

While the improved diagnosis of malformation sequences and syndromes has important consequences at the individual case level, it is equally important that the pathologist is consistently able to provide detailed descriptions of abnormalities and make intelligent overall diagnoses. This will lead to the collection of more accurate epidemiological data about the incidence and clustering of both chromosomal non chromosomal malformations lead to important questions, such as for example, those about occupational environmental teratogens, being addressed.

There is now considerable interest in the effects of paternal, as well as maternal exposure to potentially teratogenic chemicals before conception and various paternal occupations have been associated with adverse outcomes.[36] More extensive epidemiological studies are needed in this field and implicit here is the requirement for good quality pathogical data on fetuses aborted spontaneously or electively when there has been paternal exposure to putative teratogens. It hardly needs to be stressed, however, that proof of teratogenesis in human requires that a number of criteria be satisfied, including one that controlled epidemiological studies consistently demonstrate an increased incidence of a malformation spectrum in an exposed population[37,38]

Epidemiologists sometimes, however, use poor judgement when assessing malformations and classify birth defects in an inappropriate manner, for example, grouping limb reduction defects together with congenital amputations due to amniotic band sequence and leading to false conclusions about teratogens. Because of the recently emerging evidence linking limb reduction defects to chorionic villus sampling (CVS)[39], it is now recommended that all limb reduction defects in CVS exposed and non CVS exposed fetuses and babies are fully evaluated.[40]

Epidemiological studies on teratogenicity could be greatly improved if pathologists, alone or with medical geneticists and teratologists, had more input into the design, performance and analysis of these studies. Even if not formally involved in controlled studies, the expert pathologist can play a very critical role in evaluating the true incidence of certain important malformations and malformation sequences[41] and should be encouraged to do so.

The validity, usefulness and cost benefit of any regional or national birth defects or congenital malformation register is ultimately highly dependent on good quality ascertainment from all sources. It should be

remembered that one of the main goals of regional collections of data on birth defects must be to aid the investigation of avoidable factors causing birth defects and ultimately to enable collaborative research and development of prevention strategies as well as helping forecast medical and social services to accommodate changing patterns of non lethal abnormality.

Twin Studies

Scientific interest in twins and higher order multiple pregnancy has been focused on two areas in particular. One is the relative contributions of genetic and of environmental influences on development and disease, as revealed by twin studies; and the second, the specific pathology of multiple pregnancy, particularly the various abnormalities of monozygotic twinning. .It has been stated that the quality and usefulness of much of the material that has been written concerning multiple gestations is in direct proportion to the thoughtful precision and completeness of the pathological components of the descriptions and interpretations.[42]

There are several areas related to twin studies where the pathologist can play a role, though this is unfortunately not always fully appreciated by epidemiologists when twin studies are being designed or the data is being assessed. These include 1. verification of chorionicity of the placentas, 2. accurate assessment of malformations in twins, 3. documentation of the degree of concordance or discordance of these malformations, 4. verification of the sequelae of inter twin vascular communications, 5. improving the ascertainment of the different causes of excess perinatal mortality in twin pairs, and 6. clarifying the different patterns of disease at various gestational ages in like and unlike twin pairs. With the increasing availability of various forms of assisted reproduction and the subsequent increase in triplets and higher order multiple gestations, it is also important that comparable data is available in these types of pregnancies.

Placental examination is the most obvious contribution the pathologist can make to any twin study. Monochorionic placentas indicate monozygous twins and dizygosity can therefore be excluded if the placenta is pathologically confirmed as monochorionic. Twins of the same gender with single or fused dichorionic placentas may, however, be monozygous or dizygous. Most pathology associated with twinning occurs in those monozygotic twins who have monochorionic placentas with accompanying vascular connections and comprises a spectrum of abnormality ranging from inter twin vascular communication (twin-twin transfusion syndrome), so-called surviving twin syndrome with cerebral and other organ injury following intrauterine death of one of a pair of twins sharing a circulation, monoamniotic twins who have in addition a high risk of cord

entanglement and death, acardiac twin and the various bizarre patterns of symmetrical and asymmetrical conjoint twinning. In contrast, the problems of dizygous twins are usually obstetric in origin. Until prenatal ultrasound assessment of placental chorionicity becomes standard and the procedure has been sufficiently well evaluated in prospective blinded studies, routine pathological assessment of chorionicity will continue to be required.[43] In practice the only twin placentae that need to be examined pathologically (unless there are perinatal factors unrelated to twinning to be evaluated), are fused apparently single placentae of twins of the same sex.

Twin studies in general are based on the premise that by comparing a feature in monozygous and in dizygous twins, the relative contributions of genetic and environmental influences can be established.[44] In other words, studies of monozygous twins who are discordant for a given disease or malformation could, in theory provide a means of estimating the influence of early environmental factors while controlling for genetic factors. The existence of discordant malformations such as neural tube defects in monozygous twins is an obvious example and raises some interesting speculations about the differential influence of local intrauterine factors. There are, however, a number of limitations and inherent design problems in twin research and these have recently been critically discussed.[44] Furthermore, zygosity determination by blood grouping, chromosomal or DNA studies, may only be practical if reference laboratory facilities are available and the cost may be prohibitive. Placental examination may be inadequate or absent. Even in large and well designed twin studies[45], it is not always clear whether placental examination and pathogical evaluation of major fetal and neonatal abnormalities has been undertaken. The common general perinatal epidemiological problems of variable under reporting of fetal and neonatal death, and of definition of liveborn and stillborn also make comparisons of studies in different populations difficult.

Fetal and Perinatal infection

There is a small but important role for the pathologist in improving the quality of epidemiological information in this area. Underestimation of the true incidence of certain chronic and severe intrauterine infections such as congenital syphilis and congenital toxoplasmosis may occur unless a stillborn fetus or dead neonate is given a careful pathological examination. Maternal seroconversion does not necessarily mean that the fetus is infected; in the serious fetal infections such as toxoplasmosis, rubella, cytomegalovirus, varicella-zoster and human parvovirus, transplacental transmission occurs in less than one third of cases. Even if transplacental transmission occurs and the

fetus is infected, it is by no means necessarily affected and may be entirely free of the damaging tissue effects of the micro-organism at the time of birth. Even in areas of high prevalence it should not be uncritically assumed that perinatal death or specific pathology in a fetus of a mother who has seroconverted during pregnancy is a result of that disease.

Congenital syphilis can be easily missed in the macerated stillbirth or dead neonate unless one is familiar with the characteristic histopathological and radiological features of the disease which differ from those in the older infant.[46] Fetal infection with parvovirus B9 leading to hydrops and stillbirth has almost certainly been under reported in the past; pathologists are now very aware of the distinct and virtually pathognomonic viral inclusions seen in fetal tissue[47] and retrospective examination of archived tissue of hydropic fetuses using in situ hybridisation[48] has shown a considerable higher incidence of the disease than expected. In areas of high prevalence, congenital toxoplasmosis should be specifically considered at autopsy in all neonates and fetuses with a history of cerebral ventricular dilatation and periventricular echogenicity on ultrasound scan especially if signs develop rapidly.[49]

When a high prevalence of fetal disease is identified, then the cost benefit of antenatal screening in comparison with targeted educational programmes may need to be reviewed as is occurring with toxoplasmosis in France.[50]

Monitoring Outcomes of Invasive Fetal Diagnosis and Treatment

As the use of newer invasive forms of prenatal diagnosis such as chorionic villus sampling and fetal blood sampling become commonplace, it is important, both at hospital and regional level, to develop a process of formal surveillance to monitor outcomes and to identify and notify any patterns of abnormality which appear to be associated with that procedure, to enable subsequent evaluation. As well as notifying any malformations in liveborn infants subjected to invasive prenatal diagnosis, it is important that any fetus dying after an invasive prenatal diagnostic procedure be subjected to detailed pathological examination, not merely to assess obvious complications such as infection or haemorrhage but also to record any malformations, even if they are not the cause of death. As fetal therapy, including fetal surgery develop rapidly there is a good argument for formal registers, at national or international level. *Other issues related to audit of fetal diagnosis and therapy will be the subject of a further paper.*

Sudden Infant Death Syndrome in the Neonatal Period

Sudden unexpected death may occur between birth and 28 days of life. Accurate assessment of the true

incidence of Sudden Infant Death Syndrome in this period and its distinction from sudden death from identifiable causes such as overwhelming infection, unsuspected congenital heart disease, metabolic disorders and non accidental injury clearly depend, as it does in older age groups, on expert pathological examination, and usually falls into the area of expertise of the pathologist with an interest in perinatal and paediatric pathology, though in some jurisdictions the forensic pathologist may take responsibility. Since, in many countries, there are restrictions on access to this type of information and on communication between forensic pathologists and hospital pathologists, valid epidemiological data in this area of perinatal death may be difficult to obtain.

Clinical Trials with High Mortality

In randomised controlled clinical trials with an expected relatively high mortality rate, such as the ongoing United Kingdom multicentre trial of extra corporeal membrane oxygenation for acute but potentially reversible respiratory failure in the newborn, a comprehensive pathology protocol for examination of non-survivors is now regarded as essential. Should any form of fetal surgery such as repair of diaphragmatic hernia be proposed as the subject of a randomised controlled trial then a similar approach would be highly desirable.

Conclusion

Cause-specific epidemiological data can be used as a powerful tool for defining regional and national goals in health care and for guiding the development of new services and of prevention strategies in general[4] and in perinatal medicine in particular. The pathologist can play a central role in ensuring that this data is of highest achievable quality, both by encouraging autopsies where practical and where not by actively promoting the use of alternative means of investigating perinatal disease.

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