Perinatal Pathology

1

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To the mothers and fathers who have lost their loved child: we try to heal.

1.1 Global Burden of Disease

For all age groups, neonatal disorders ranks as first and congenital birth defects ranks as tenth leading cause of disability adjusted life-year in the Global Burden of Disease study in the latest iteration, for data for 2019 [1]. Neonatal disorders accounted for 1.78 million deaths (95% UI (uncertainty interval): 1.70–1.86) in 2017 [2]. Neonatal disorders encompassed neonatal preterm birth complications, neonatal encephalopathy due to birth asphyxia and trauma, neonatal sepsis and other neonatal infections, hemolytic disease and other neonatal jaundice, and other neonatal disorders. In 2019, globally, 2.4 million deaths occurred in the first month of life. Two regions account for almost 80% of all neonatal deaths in 2019; sub-Saharan Africa accounted for 42% and Central and Southern Asia accounted for 37% of all such deaths [3].

In 2019, an estimated 2 million babies (90% UI: 1.9, 2.2) were stillborn [4]. UN IGME stillbirth estimates refer to deaths occurring at or after 28 weeks of gestation, which is in-line with the International Classification of Diseases, but underestimates the real burden of stillbirths, since it excludes stillbirths occurring at earlier gestational ages. National stillbirth rates around the globe ranged from 1.4 to 32.2 stillbirths per 1000 total births in 2019. An estimated 84% of all stillbirths in 2019 occurred in low- and lower middle-income countries, while those countries only accounted for 62% of live births. By contrast, high-income countries accounted for just 2% of the global burden of stillbirths but constituted 9% of live births worldwide. Sub-Saharan Africa (42% of global burden), followed by Southern Asia (34%), had the highest stillbirth rate and the greatest number of stillbirths. Six countries bore the burden of half of all stillbirths—India, Pakistan, Nigeria, the Democratic Republic of the Congo, China and Ethiopia, in order of burden [4].

The prevalence of stillbirths and terminations of pregnancy after a diagnosis of fetal anomaly (TOPFA) in Europe in 2013–2019 was about 4.5 and 54.0 per 10,000 births respectively [5]. With about 4.2 million births in the European Union in 2019 [6], this equates to about 1890 fetuses with fetal anomalies who were stillborn and 22,600 such terminations per year. Only about 7% of stillbirths are reported as being due to congenital abnormalities [4, 7]. The proportion of stillbirths relating to congenital abnormalities in low and middle income countries is unknown.

TOPFAs differ from the approximately 73 million abortions from roughly 121 million unintended pregnancies that occur each year [8].

1.2 Perinatal Pathology

Perinatal pathology is the study of disorders of the placenta, fetus and neonate. The Royal College of Pathologists (UK) states that a "fundamental part of a perinatal pathologist is to conduct autopsies on fetuses and babies who are stillborn or die shortly after birth" [9]. They also examine tissue samples taken from living babies and infants at biopsy or operation [10]. Thus, the perinatal pathologist would be ideally placed to investigate this worldwide large burden of disease.

Pathology workforce, however, may not facilitate this. Apart from China, the six countries with the highest numbers of stillbirths are limited by the number of physicians (Table 1.1) [11], of whom only a small proportion are pathologists if data from other countries (Table 1.2) [12] are extrapolated.

Data on number of pathologists may be challenged [13] but not all pathologists practise as perinatal pathologists. Perinatal pathologist numbers are counted as pediatric pathologists as most perinatal pathologists have specialized

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training in either gynecologic and/or pediatric pathology and perinatal pathology is part of training in pediatric pathology [14]. It then becomes obvious that the number of subspecialist perinatal pathologists are diminishingly few. The Royal College of Pathologists (UK) lists 64 pediatric pathologists out of their 3091 consultant pathologists in United Kingdom [15]. (Fig 1.1) In USA, there are 268 pediatric pathologists out of 21292 pathologists according to American Medical Association listing of all pathologists [13]. Notwithstanding that these figures differ from other sources regarding the total number of pathologists (2271 in UK, 12839 in USA), [12] there is no resiling from the small numbers of perinatal/pediatric pathologists practising even in high-income or resource-rich countries.

Anatomical pathologists who provide a predominantly biopsy-oriented service, focused on identification of cancers, often fail to appreciate the extent and burden of perinatal losses—2.4 million deaths within the first month of life and 2 million stillbirths in 2019. By comparison, in 2018, the five commonest cancer deaths accounted for approximately 4.5 million lives (1.76 million lung, 782,000 stomach, 781,000 liver, 626,000 breast and 551,000 colon) [16]. Medical workforce shortages in pathology, coupled with increasing anatomical pathology workloads, have resulted in neglect of the perinatal autopsy or its lower priority.

Table 1.1 Physicians per 1000 people

Countries with most numbers of stillbirths	Physicians per 1000 people	Countries ranked in order of most physicians per 1000 people	Physicians per 1000 people
India	0.9	Cuba	8.4
Pakistan	1.0	Georgia	7.1
Nigeria	0.4	Lithuania	6.4
Democratic Republic of Congo	0.1	Greece	5.5
China	2.0	Austria	5.2
Ethiopia	0.1	Portugal	5.1

Data from 2016 to 2018 [11]

Unless a proper scrutiny of the varied and complex scope of the perinatal autopsy is undertaken [17], the perinatal autopsy can be so easily devalued. Determining whether an anomalous finding is part of an established syndrome or malformation can be time-consuming, sometimes taking longer to search the extant literature than to undertake the autopsy itself. Documenting the findings accurately is so important as it allows correlation of phenotype with genetic information and may determine if variants of uncertain significance are pathogenic. Undervaluing the professional effort in perinatal autopsy leaves the service vulnerable to further under-resourcing; in many jurisdictions, including UK, USA and Australia, these procedures are not reimbursed.

1.2.1 The Perinatal Pathologist as a Treating Physician

There are many factors that affect parents' decisions to consent to an autopsy [18–23]. Women who consented to post-mortem examination were more likely to be counselled by a senior staff member than by junior medical staff or midwifery staff [24].

The afore discussion of pathologists as physicians is very relevant in the context of a perinatal autopsy service. Perinatal pathologists who have expert knowledge about the autopsy process and have positive views regarding its value rarely see parents; of the 21 pathologists out of 40 pathologists who responded to a survey about the perinatal autopsy, 13 reported that they never saw parents to discuss the autopsy [19].

It is inconceivable that patients would consent to a surgical procedure without having spoken with or discussed the procedure with the surgeon, and be informed directly by the surgeon about the risks, benefits and expected or unexpected outcomes. Why would pathologists think they are not treating physicians or been made to think so? Why would they consider themselves to be merely technicians to whom the autopsy has been delegated by the "clinician" to perform? Some pathologists clearly see the value of being a treating

Table 1.2 Number of pathologists and proportion to physicians

Selected other countries/ regions	Number of pathologists	Pathologists per 1000 people	Physicians per 1000 people	Proportion of pathologists to physicians
United Kingdom	2271	0.035	2.8	1:80
United States of America	12839	0.039	2.6	1:70
Canada	1767	0.048	2.6	1:49
Germany	1692	0.021	4.2	1:200
European Union		0.031	3.7	1:120
OECD countries			2.9	
Sub-Sahara Africa			0.2	
South Asia			0.8	

Data from [11, 12]

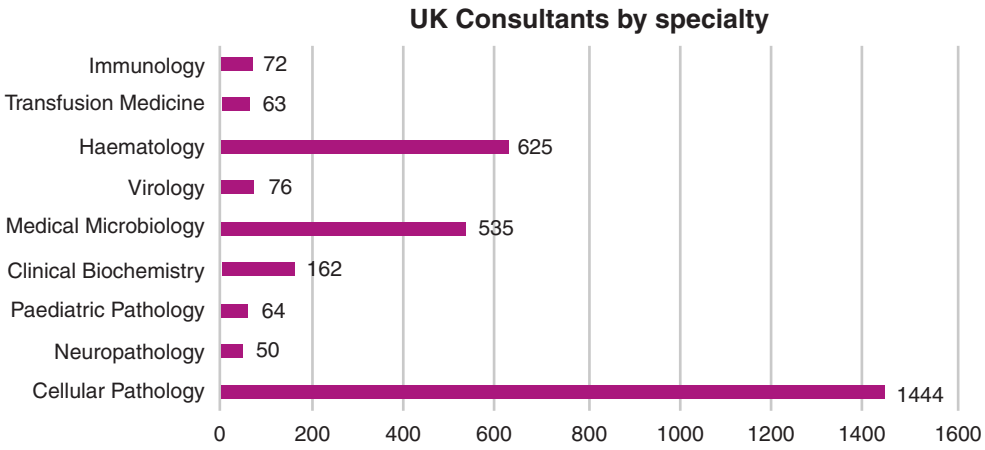

Fig. 1.1 Number of consultant pathologists in United Kingdom by subspecialty. Reproduced with permission from Royal College of Pathologists (UK) [15]

physician and do see and counsel parents about the perinatal autopsy [20, 25–27]. A counter argument is that many pathologists did not enter the specialty with a desire or ability to embark on negotiations with grieving relatives and social workers [28]. Discussing the autopsy may be difficult but need not be a daunting task [29]. There is no denying that clinicians who already have a relationship with the family are best placed to request the autopsy. However, clinicians consistently report low levels of understanding of the procedure [19, 30]. Pathologists educating those who seek consent about the post-mortem examination process have improved consent rates [24, 31].

Caring as a treating physician does not end with the performance of the autopsy. It has been posited that the pathologist has a central role to play in explaining the autopsy findings to next of kin and that such a valuable service should be part of every pathologist's normal practice and be available to all next of kin upon request [32]. This would accord with one study that found that a quarter of parents would have appreciated the opportunity to talk to the pathologist who performed the autopsy [21]. Pathologists can also lend support to bereaved parents and communities by meeting them informally [27].

Women who have experienced a perinatal loss report high Perinatal Post Traumatic Stress Disorder scores [33]. The short time between delivery and loss does not offer sufficient opportunities to create memories for families, and one way of doing so is for pathology departments to create these for the families [27, 34]. These activities are not "core business" of anatomical pathology departments but should be for those offering a perinatal autopsy service.

1.2.2 The Perinatal Pathologist as a Diagnostic Clinician

The neonate is not a small child and the child is not a small adult. Tissue that may be procured in larger sizes or more easily, without anesthesia in some cases, in older patients are generally not the case in neonates. The image of the anatomical pathologist wedded to the microscope pursuant to diagnosing an entity on a glass slide is an anachronism. The perinatal pathologist has a key role in the clinical management of the child by participating in deciding how the tissue could be best used given the amount may be small and there are various test methods [35]. Discussion of the case with surgeons, genetic pathologists, clinical geneticists, radiologists, microbiologists, amongst others, can be time-consuming, however, but are nevertheless essential to deliver an excellent service. These activities are usually not reflected in the metrics of workload of a pathologist if number of biopsies are the basis on which laboratory activity is assessed and renumerated.

1.2.3 The Perinatal Pathologist as a Clinical Manager

Health care funding varies enormously between countries (Table 1.3) [36]. Laboratory testing remains a small portion of health care expenditures [37]. How much of that filters through for investigating the burden of perinatal disease is not known.

The cost of stillbirth investigations in United Kingdom in 2012 was estimated at £1804 (2020 AUD4218) [38] and in Australia in 2020 to be AUD4246 [39]. Mistry et al. modeled care in subsequent pregnancies and found that care for women with a previous stillbirth with an unknown cause (£3751) was more costly than for women with a history of stillbirth from a non-recurrent cause (£3235) or a known recurrent cause (£3720), [38] therefore offsetting the cost of a postmortem examination in a stillbirth by altered pattern of care in a subsequent pregnancy.

The main cost drivers for investigation of stillbirths were having an autopsy or cytogenetics [39]. With regard to the latter, microarray has replaced conventional karyotyping in

Table 1.3 Current Health Expenditure

	Health expenditure per capita (PPP current international $)	Health expenditure as % of GDP
Countries with most numbers of stillbirths		
India	275.13	3.54
Pakistan	178.24	3.20
Nigeria	232.99	3.89
Democratic Republic of Congo	30.72	3.30
China	935.19	5.35
Ethiopia	66.64	3.30
Countries by income		
High income	5971.68	12.42
Middle income	647.09	5.41
Low income	218.95	5.34

GDP Gross domestic product, *PPP* purchasing power parity
Data from [36]

most laboratories as it provides a result more frequently than karyotyping and better detection of genetic abnormalities [40]. Again, the perinatal pathologist has a key role in managing resources. For example, further genetic sequencing testing following a perinatal loss, including whether to perform trio testing, may yield additional prognostically relevant information but inter-disciplinary discussion with the genetic pathologist, clinical geneticist and obstetrician or neonatologist regarding the cost-benefit yield will determine the course of further investigations.

1.3 Water-Shed

Advances in several fields, particularly in medical imaging and genomics, have led to changes in the practice of perinatal pathology, which has reached a Schumpeterian moment (see also Chap. 2: an evolving practice). The classical conventional autopsy may no longer be a gold standard in future. Perinatal pathologists have a continuing major role to help nurture the subspecialty for the benefit of parents and their children.

Preliminary studies from dedicated expert centers show good correlation between interpretations from imaging techniques [41–43]. Medical imaging is rapidly expanding its training of practitioners in the skills of interpreting in utero and post-delivery perinatal images (see Chap. 5). The test will be how well imaging performs in the real-world away from the few dedicated centers and hence there will be a continued need for correlative audit studies. It is probable that with increased experience, the area under the receiver operator characteristic curve will increase with increasing familiarity of the technique, in a way similar to introduction of other new health technologies.

Genomic sequencing technologies (see Chap. 3) continue to yield information regarding likely genetic causes for stillbirths, neonatal deaths, and structurally anomalous fetuses [44–47]. The list of pathogenic variants continues to expand. As alluded earlier, the contribution of the perinatal pathologist and the classical autopsy is crucial in carefully documenting structural and developmental anomalies that may help in determining the likelihood of variants of uncertain significance being pathogenic. The use of the molecular autopsy has clinical utility in assessing recurrence risks, and helping management in subsequent pregnancies, including use of pre-implantation genetic diagnosis.

In the near future, the place of these various diagnostic modalities will likely be determined. One approach may be better diagnostically and prognostically than another depending on characteristics of the loss, such as degree of maceration, prior obstetric history, organ system(s) of anomaly, amongst other factors.

For parents and healthcare providers alike, discussion around consent to a perinatal postmortem examination will need to be nuanced, for example, with alternative diagnostic approaches, sequence of testing, likelihood of yield of clinical information, and clinical utility of the information, timeliness, and parental wishes and expectations.

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