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Lecture 12b: Congenital Malformations, Stillbirths and Perinatal Deaths

Congenital Malformations

Definition Congenital Malformations

- Anomalies of structure or function of the fetus which occur before birth
- **Major Birth Defects**
 - Anomalies requiring medical/surgical treatment or entailing significant handicaps, diagnosed at birth or during childhood
- **Minor Birth Defects**
 - Developmental anomalies present at birth, but not requiring intervention or causing handicaps.

Childhood Cancers

- Cancers in childhood may have fetal origin and may be a result of intrauterine exposures
 - Childhood leukemia
 - Brain cancers
 - Neuroblastoma

Diagnosis of birth defects

- Diagnosis depends on severity and intensity of investigation:
 - External anomalies usually detected at birth
 - Internal anomalies harder to diagnose
Anomalies threatening survival or causing morbidity in newborn usually diagnosed earlier
 - Occult anomalies often not diagnosed before childhood or even adulthood (e.g., cardiovascular anomalies)

Sources of Data

- Birth certificates
 - variable quality of diagnosis
 - limited to anomalies discovered at birth,
 - no information on anomalies diagnosed at later ages
- Surveillance (e.g., CDC birth defects registry, Hungarian registry etc)
- Specialized studies

Problems of measurement

- Many congenital anomalies result in spontaneous abortion or stillbirth
- Most diagnoses in live born represent selective survival
- Many anomalies do not present until latter age of childhood (e.g., CVD)

Congenital Malformations

- Prevalence
 - 3% major (live births) additional ~3% diagnosed at later ages
 - 10% minor (live births)
- Prevalence declines with duration of pregnancy, due to selective survival

Distribution of Severity

(Czeizel BMJ 1993;306:499)

Hungarian registry data

- Lethal
 - Rate 0.6%
 - 9% of anomalies
- Severe
 - Rate 1.9%
 - 30% of anomalies
- Mild
 - Rate 4.0%
 - 61% of all anomalies

Preventable anomalies ~ 70%?

Timing/Causes of Congenital Malformations

- Timing of occurrence/causal exposure
 - Pre-conception
 - Genetic (point mutations)
 - Chromosomal anomalies (trisomy, deletions, polyploidy)
 - At conception (chromosomal abnormalities)
 - During gestation (chromosomally normal)
 - Organogenesis (<12 weeks) teratogens
 - Post-organogenesis functional defects
 - Deformations

Genetic and Chromosomal Defects

- **Genetic mutations**
 - rate ~ 2.25/1000 live births
 - 7.5% of all malformations
 - Increase with paternal age
- **Chromosomal Anomalies**
 - Rate 1.8/1000 live births
 - 6% of all defects
 - Increase with maternal age
- **Chromosomal anomalies:**
 - 40% spontaneous abortions
 - 6% stillbirths,
 - <1% live births

Source: Kalter NEJM 1983

Disorders of Organogenesis

“Teratogenesis”

- Agents which disturb organ development are teratogens.
- Malformations are multicellular disorders
- **Critical timing**; effects only observed at specific times in organ development
- Most teratogens show a “**threshold**” or “all or none phenomenon”
 - Most teratogenic agents have no effect below a particular exposure dose
 - Teratogenesis incidence and severity tend to increase above threshold in a dose-response manner
 - Percent of embryos affected increases with dose

Teratogens

- **Drugs** (thalidomide, anticonvulsants, bendectin, anesthetics)
- **Medical treatments**
 - IVF, ICSI
- **Radiation**
- **Maternal infections** (rubella, CMV, Toxoplasma)
- **Maternal illness** (Diabetes, thyroid deficiency)
- **Environmental/occupational exposures**
 - Heavy metals (lead, cadmium, mercury)
 - Organic solvents, pesticides, dioxin
- **Personal habits**
 - Alcohol ? Fetal alcohol syndrome?

Examples of threshold effects

- **Thalidomide**
 - 50 mg thalidomide during critical period of limb development affects the majority of embryos
 - 0.5 mg no effect
- **Radiation**
 - 100 rads malform 90% of embryos
 - 1 rad no effect

Organogenesis

Timing of Exposures

- Most organogenesis completed by 12th week in humans
- Critical period of susceptibility varies between organ systems
- Dose dependent effects (e.g. embryo/fetal death, structural defects)

Formation of organ systems

- Cell proliferation, migration, differentiation, induction, programmed cell death (apoptosis), developmental fields, effects on adjacent organ
- Animal models differ from humans (timing, susceptibility), need multiple species studies, and multiple generation studies

Malformation, deformation and disruption

- **Malformation** is a defect of organ formation which can lead to subsequent deformation or disruption
 - spina bifida → hip dislocation and club foot
- **Deformation**
 - Uterine constraint → club foot
- **Disruption**
 - Amniotic rupture → amniotic bands → limb constriction/amputation

Classifications of Congenital Malformations

- Lumping vs. splitting of outcome
- Single defects vs multiple defects (single defects rarer)
- Organ system,
- Embryonic layer (mesoderm, ectoderm, endoderm)
- Syndromes (e.g. Downs, one etiology → multiple organ system effects CNS, CVD)

Animal Studies of Birth defects

Animal Studies (teratogenicity, toxicology)

- Can experimentally control dose and timing of exposure
- Can differentiate between maternal toxic effects and teratogenic effects
- Intergenerational effects
- Generalizability to human exposure?? (e.g., thalidomide in rat or rabbit not teratogenic at human dose)

Toxicity Studies

Possible adverse effects:

- **Generalized toxicity** (e.g. non-specific maternal effects)
- **Developmental toxicity** in the absence of maternal toxicity is greatest concern
- **Adverse effects depend on timing of exposure:**
 - Embryonic period (< 8 weeks postconception) affect organogenesis, structural defects pregnancy loss)
 - Fetal period (intrauterine growth, developmental abnormalities, fetal loss)
 - Preconceptional gametogenesis (eg. gene mutation)
- **Reproductive effects** (e.g. hormone exposures, endocrine disruptors)
- Induction of **childhood cancers**

Human Studies

- Problems
 - Rare events
 - Effects may be only on specific defects (uncommon)
 - Classification of defects problematic
 - Easier to detect risks with unusual defects than with more common defects (e.g., thalidomide)

Exposure measurement and teratogenicity

Refinement of exposure

– Dose/timing

- Amount during entire pregnancy?
- Amount during critical developmental period?
- Total amount, average amount, or maximum dose?

– Problems

- Recall or measurement biases
- Medicolegal and media environment (bias)

Congenital Malformations

Refinement of exposure

– Stage of gestation

- Early blood glucose control with diabetic mother prevents adverse effects
- Folic acid and neural tube defects
- Bendectin and pyloric stenosis
 - problem one of the most commonly used drugs in early pregnancy in 1980s, massive publicity, selective recall and other bias, lack of consistency between studies

Congenital Malformations Study of Live Births

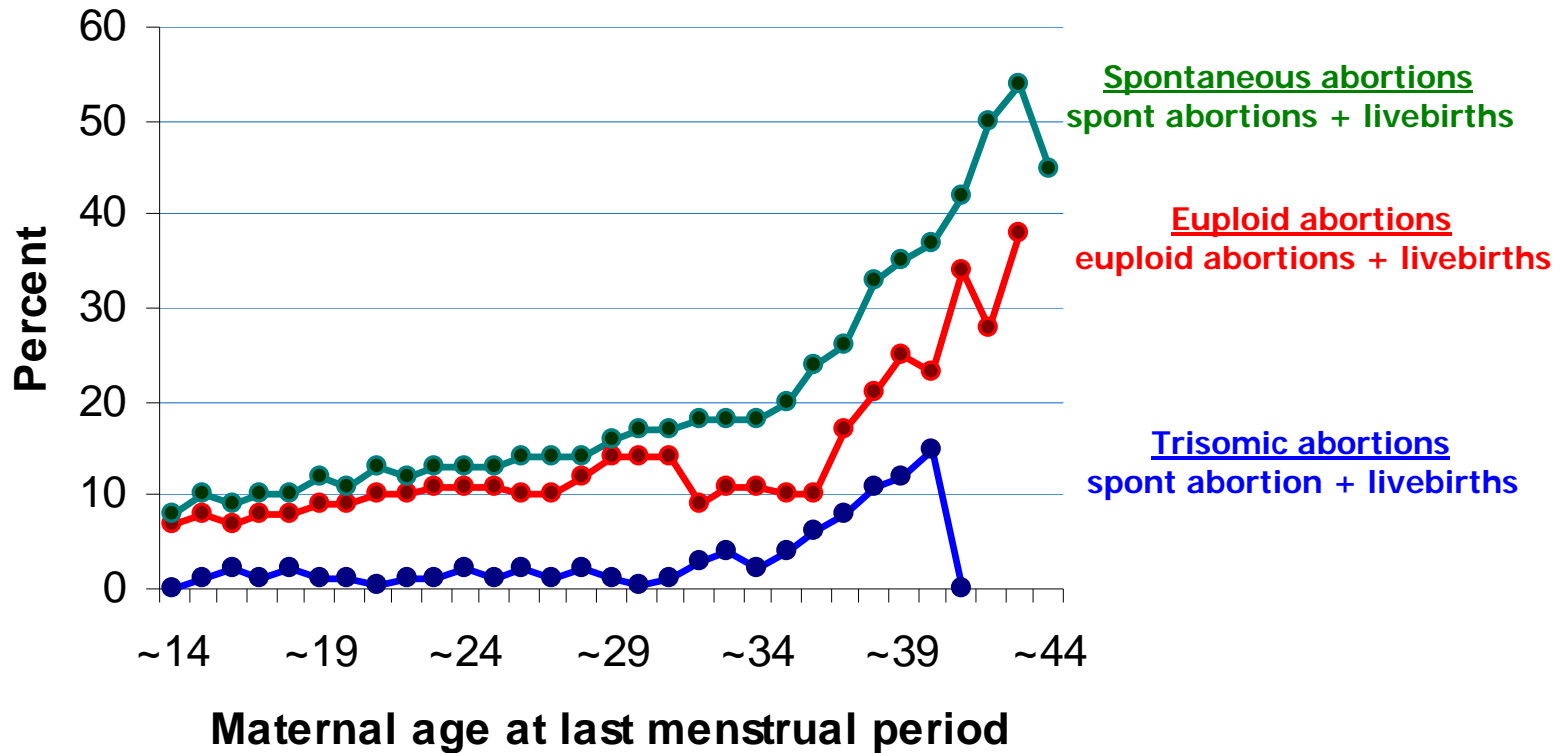
- **Why use births?**
 - Accessible to clinical observation
 - Systematically recorded
- **Problems**
 - Lack of statistical power
 - Incomplete
 - Excludes defects incompatible with live birth
 - Misleading because don't know pattern of loss between conception and birth (prevalent surviving cases)

Congenital Malformations

Study of Spontaneous Abortions

- **Why study SABs?**
 - Wider range of malformations
 - Closer to time of origin
- **Problems**
 - Still limited to prevalent cases
 - Selection bias
 - Early losses are underrepresented
 - Missing fetal tissue more often in earlier gestation
 - Women who miscarry earlier less likely to get care
 - Cannot establish reliable diagnosis
 - Difficult to obtain tissue

SAB Rates by Age



Estimated rates (%) of spontaneous abortion, euploid abortion and trisomic abortion by maternal age for public patients

Non-Chromosomal Abnormalities and Age

(Hollier *et al Obstet Gynecol* 2000;96:701)

Rates of non-chromosomal abnormalities
per 100 births or abortuses by maternal age

20-24 %	25-29 %	30-34 %	35-39 %	40+ %
3.5	3.9	3.9	4.4	5.0

Sex ratio at birth to infer earlier losses

- **Dioxin exposure Seveso, Italy** (Mocarelli Lancet 2000)
 - Paternal dioxin levels associated with reduced male sex ratio (0.38 CI 0.3-0.5) vs unexposed sex ratio 0.55
- **PCB exposures Japan** (Occup Env Hlth 2001)
 - No effect on sex ratio (0.51)
- Sex ratio may be a marker of selective toxic exposures in utero

Anticonvulsant drugs

(Holmes *NEJM* 2001;344:1132)

- **Anticonvulsant embryopathy**
 - Major malformations, growth retardation, facial and finger hypoplasia
 - Is this caused by epilepsy or by drugs?
- Screened 128,000 pregnant women
- 223 exposed infants vs 508 controls
 - Embryopathy in 20.6% of exposed to one anticonvulsant vs 8.5% in controls
 - Embryopathy in 28.0% of exposures to two or more drugs
 - Mothers with history of epilepsy but no drugs, embryopathy same as controls

Late onset and intergenerational effects:

- **Diethylstilbesterol (DES)** Used for prevention of threatened miscarriage
 - Clear cell vaginal carcinoma in daughters
 - Increased breast cancer risk in daughters
 - Increased preterm birth, ectopics and pregnancy loss in daughters pregnancy
 - Decreased sperm in sons
 - Increased testicular cancer in sons?

Ecologic Studies

- Chernobyl
 - Childhood leukemia in Finland – no effect observed
 - Trisomy 21 in Berlin, cluster of 12 cases in January 1987 (expect 2-3).

Deformations

- **Misoprostol (prostaglandin)** used for induced abortion in Brazil
- **Mobius syndrome:** facial paralysis with or without limb constriction defects
- OR = 30 with misoprosotol exposure
- Due to constriction caused by uterine contractions

– Pastuszak *NEJM* 1998;338:1881

Functional Neurologic Abnormalities (post-organogenesis)

- Cerebral palsy (CP)
- Cystic periventricular leukomalacia
cPVL
- Mental retardation
- Other neurologic abnormalities (e.g.
strabismus)

Neurologic Abnormalities and Immune activation

- Neurologic abnormalities increasing with increased survival of preterm births
- Evidence that immunologic factors particularly fetal response play a role
 - IL-1 and TNF- α inflammatory cytokines produced by stress and infections, affect brain by ischaemia/hypotension, cause cell death
- Cystic periventricular leukomalacia (cPVL) in new born (damage to white matter) associated with cerebral palsy and cognitive disorders

Meta-analysis

Chorioamnionitis and Cerebral Palsy

(Wu *JAMA* 2000;284:1417)

- Chorioamnionitis and cerebral palsy RR = 1.9 (1.4-2.5)
- Chorioamnionitis and cystic periventricular leukomalacia (cPVL) RR = 3.0 (2.2-4.0)
- Chorioamnionitis and/or cPVL adjusted for gestational age RR = 1.8 (1.3-2.4)

Case Control Study of Chorioamnionitis and Cerebral Palsy (JAMA 2003;290:2677)

- Chorioamnionitis in cerebral palsy (CP)
= 14%, control 4%,
- Adj OR = 4.1 (1.6-10.1)

Perinatal Mortality

- Perinatal mortality rate (PNMR) = late fetal deaths plus early neonatal deaths/live and stillbirths
 - Late fetal deaths > 20 weeks gestation (US)
 - Late fetal deaths > 28 weeks (WHO international comparative data)
 - Early neonatal deaths < 1 week of life

Why Perinatal mortality

- Indicator of obstetric care and deaths later in pregnancy, intrapartum, post-delivery
- Avoids the problem of differentiating live from stillbirths
- Traditionally associated with “asphyxia”

Causes of Perinatal death

- Preterm delivery LBW
- Respiratory distress syndrome
- Congenital anomalies
- Birth trauma/asphyxia (prolonged labor, hemorrhage, multiple pregnancies)
- Infections (syphilis, HIV)
- Sepsis (B hemolytic strep)
- Hypothermia

Neonatal Mortality

- Neonatal mortality rate (NMR) = deaths among live born infants prior to the first 28 days of life, per 1000 live births
- Early Neonatal mortality (ENMR) = deaths 0-6 days
- Late Neonatal mortality (LNMR) = deaths 7-28 days

Neonatal deaths world wide

Lawn *Lancet* 2005;365:891

- ~ 4 million deaths
- 38% of child deaths
- 75% in 1st week of life
- 99% in developing countries
- Main causes
 - Preterm birth (28%)
 - Infections 26%
 - Asphyxia 23%
 - Tetanus 7%

Causes of Non-Infectious Neonatal Deaths During Pregnancy and Delivery

- **Birth Outcomes**
 - Low birth weight
 - Preterm delivery
 - Birth defects
- **Obstetric and Neonatal Complications**
 - Injury/asphyxia
 - Hypothermia
- **Maternal Health** Preceding and During Pregnancy

Infectious Causes and Prevention of Neonatal Deaths

- **Bacterial Infections**

- Sepsis (Group B Streptococcus)
- Respiratory infections
- Tetanus
- Diarrhea
- Meningitis

- **Viral Infections**

- HIV
- HSV-2
- CMV

- **Malaria**

- **Prevention of infection**

- immunization
- prophylaxis via antibiotics or antiseptics
- Malaria prophylaxis /control
- Cord care (tetanus)
- Treatment of infections in new born
- Aspesis/Cleansing of birth canal
- C section

Problems with measurement

- Under registration in LDCs
- Definition of a live birth problematic.
 - Omission of infants who die shortly after birth affect numerator and denominator of NMR
 - Variation in definition of “live birth” (e.g., USSR)
 - Advantage of PNMR
- Cause of death poorly reported
 - Autopsy in DCs
 - Verbal autopsy (interview) in LDCs

Neonatal Mortality and Contribution of Infection: Community Studies in Developing Countries

(Stoll *Clinic Perinatol* 1997;24:1)

• Neonatal Mortality/1000 LB	• Proportion due to Infection (%)
Africa 9-65/1000	9-54%
S. Asia 19-89/1000	8-64%

Neonatal infection is probably the major preventable cause of neonatal death in less developed countries

Trials to reduced neonatal mortality in developing countries

- India: Improved neonatal care reduced neonatal mortality (Bang Lancet 1999)
- Malawi: Genital tract cleansing with chlorhexidine reduced neonatal sepsis and mortality (Taha BMJ)
- Nepal: Chlorhexidine washing of cord or baby reduced neonatal sepsis and tetanus

Neonatal tetanus

- Defined syndromically
 - Normal suckling and crying followed by an inability to suck or cry; onset 3-10 days of age
 - Spasms, stiffness, convulsions
- ~ 450,000 cases per year
- case-fatality ~75%
- Preventable by immunization of mother and cord care

Figure 1a: Levels and Medium-Term Trends in Neonatal Mortality in Asia

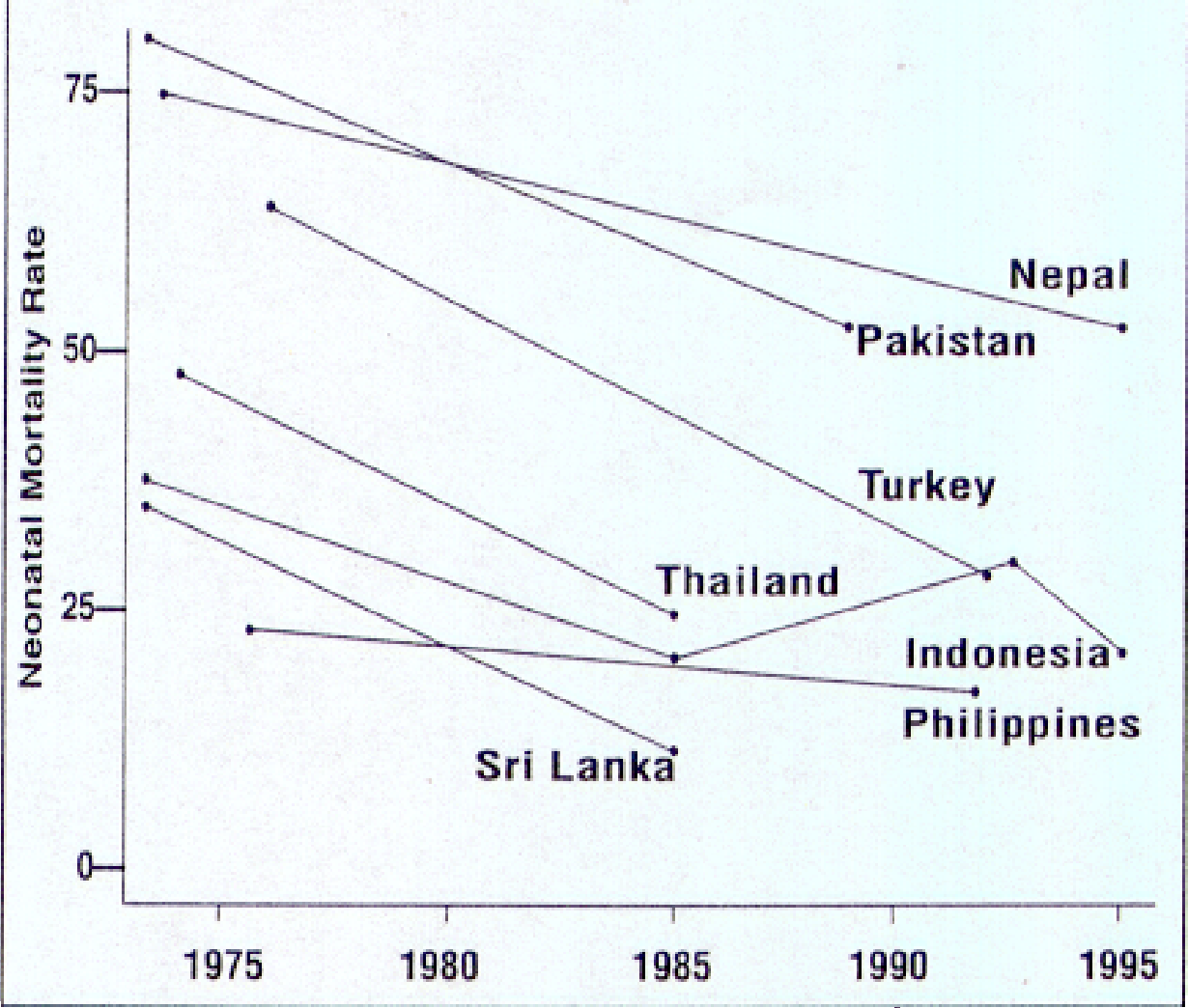


Figure 1b: Levels and Medium-Term Trends in Neonatal Mortality in Latin America

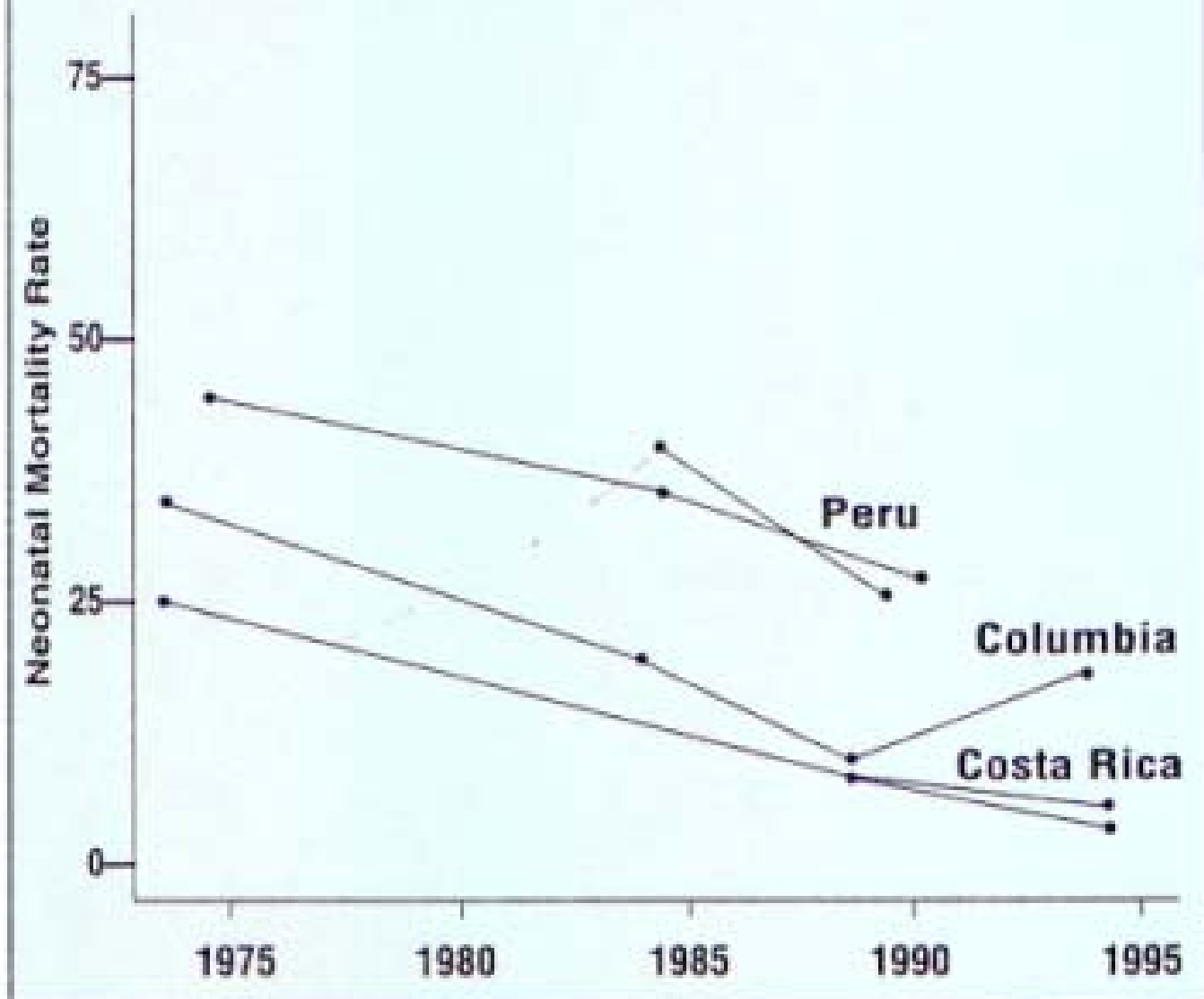
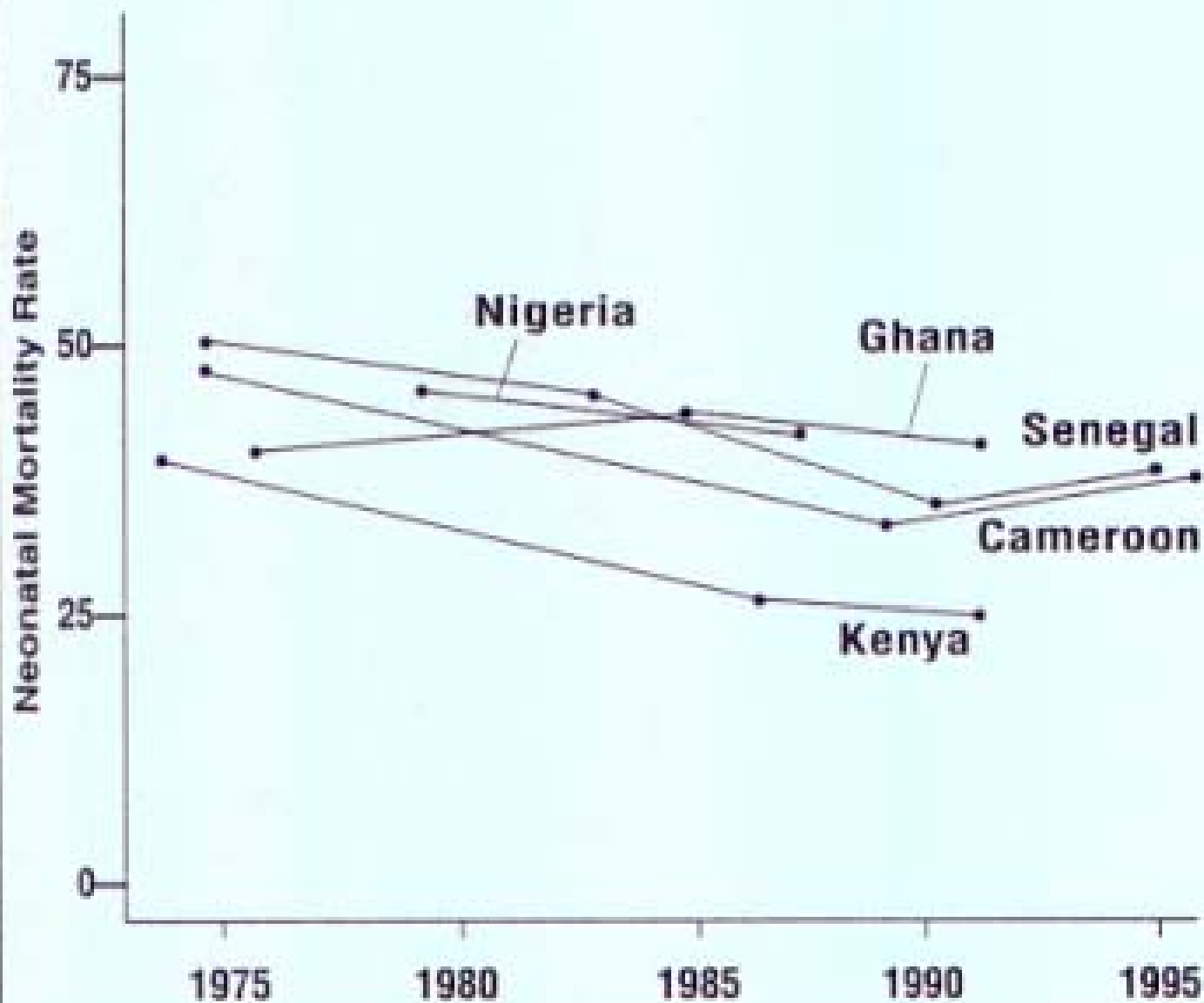


Figure 1d: Levels and Medium-Term Trends in Neonatal Mortality in Sub-Saharan Africa



Neonatal Mortality and Infant Mortality

- Where IMR is high, more deaths occur in the postneonatal period
- As Infant mortality (IMR) declines, NMR and particularly ENMR constitutes a greater proportion of deaths in infancy
- Declines in IMR shift focus of prevention to NMR