Prospects for Research in Reproductive Health and Birth Outcomes

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Global population reached 1 billion in 1800, 2 billion by 1930, 3 billion in 1960, 4 billion in 1975, 5 billion in 1987, and 6 billion in 2000.1 With the world population doubling every 30 to 40 years, environmental damage becoming more apparent, fresh water and fossil energy supplies diminishing, and one third of all people malnourished, overpopulation is among the biggest threats to human existence. Overpopulation is not evenly distributed across the globe: many geographic areas in North America, Europe, East Asia, and Australia have achieved nearly stable populations, whereas parts of Africa, Asia, and South and Central America have population doubling every 20 to 25 years.2 In many of these countries, more than half of the population is younger than 15 years and nearly ready to have children of their own.

The discrepancies in fertility rates and reproductive outcomes between developed and developing countries are profound. The average number of births to each woman in most developed countries is 1.5 to 2 vs 3 to 7 in many developing countries.2 In most industrialized countries, fewer than 10 in 100,000 women die in childbirth, while in many developing countries, 1% of women die of childbirth-related causes.3 In some developing countries, the lifetime risk of death associated with childbearing is 1 in 20.4 Five to 8 infants per 1000 die in the first year of life in many developed countries, but 50 to 150 infants per 1000 die during the first year in many developing countries.5 In some developing countries (such as Malawi, Kenya, Senegal, and Yemen), nearly half the women have experienced the death of at least 1 child.6 Until now, malnutrition, various bacterial infections, and lack of access to basic obstetric and pediatric care have explained most of the differences in infant mortality rates.7 However, in some developing countries, especially those in sub-Saharan Africa, HIV (human immunodeficiency virus) now infects one third of all pregnant women.8 With HIV transmission to the infant occurring in 25% to 35% of births, either during delivery or with breastfeeding, those countries are experiencing a sharp increase in infant and childhood mortality. In most industrialized countries, only about 1 in 1000 women is HIV-infected and antiviral therapy diminishes maternal-to-infant transmission.9 During the last 5 decades, several factors have improved reproductive outcomes in developed countries. These include lowered birth rates due to advances in contraception, including the estrogen-progestin pill, depoprostegins, intratubal contraceptive devices; safer abortion procedures; and safe tubal ligations. Improved access to safe cesarean delivery, blood banking, antibiotics, and better management of preeclampsia have made childbirth almost routine and generally safe for the mother. Infant mortality has also declined in developed countries. Vaccination for childhood diseases, antibiotics for bacterial infection, supine rather than prone sleep position for the prevention of sudden infant death syndrome, and newborn intensive care for preterm babies have reduced infant mortality. In some developing countries, infant and childhood mortality has been reduced with the use of similar interventions plus oral rehydration therapy for diarrhea. However, in some areas, these interventions are rarely or incon-
sistantly available, and infant mortality rates continue to be high.

Maternal mortality rates are also high in many developing countries, and ma-
ternal mortality rates worldwide have not decreased in the last 10 to 20 years.10,11 This lack of improvement is primarily due to many of the interven-
tions known to reduce maternal mor-
tality in developed countries not being routinely available in many developing
countries.4,10,11 Since the catastrophic
events leading to maternal death are not easily predicted and because rapid trans-
fer to a capable health care provider is
often not feasible even over relatively short distances, creation of a system of
care that provides women timely ac-
cess to life-saving interventions should
be 1 of the highest health priorities in
developing countries.10,12

Care for the infant immediately after birth is also commonly neg-
glected.17 While infant mortality dur-
ing the first year of life has decreased in many developing countries, deaths in the immediate neonatal period have de-
creased only slightly or not at all. Ob-
stetric interventions that result in less asphyxia and infection, newborn resus-
citation, and treatment of childbirth complications, such as infection, are of-
ten not available. In developing coun-
tries, most deaths in the first year of life occur in the first hours and days after
delivery.7 As with skilled obstetric care that saves the lives of mothers, a trained attendant present at birth can save the
lives of many infants.

Reproductive Health Outcomes
Adverse Health Behaviors. Many re-
productive health problems in indus-
trialized countries originate with ad-
verse maternal behaviors. For example,
more than half of pregnancies in the United States are unplanned, with many
also unwanted.13 In the United States, 1.5 million women undergo elective
pregnancy terminations each year.14
One in 5 pregnant women smoke, ac-
counting for more than one third of all growth-restricted infants, and use of al-
cohol and other drugs during preg-
nancy causes an unknown burden of
fetal alcohol syndrome and other child-
hood morbidities.15,16 With the excep-
tion of some modestly effective anti-
smoking interventions,17 little in the
way of effective prevention or treat-
ment for these problems is available.

Infertility. There have been major ad-
vances in reproductive medicine in the
last several decades. In the 1960s, the
sequence of physiologic events in the nor-
mal menstrual cycle and during preg-
nancy was characterized. This knowledge
led to the successful use of various hor-
mones or their analogues for ovulation
induction. The combination of ovula-
tion induction and in vitro fertilization
(IVF) of the harvested ova resulted in the first “test tube” baby in 1978. During the
last 20 years, refinements in ova harvest-
ing and embryo culture techniques have
led to a steady increase in pregnancy
rates. The use of donated ova and sperm
is now well established. Increased use
of IVF has been accompanied by substan-
tial decreases in various types of fallo-
opian tube reconstructive surgery that was
previously performed to improve ferti-
lity rates.

Unfortunately, many pregnancies
achieved following ovulation induction
or IVF have 3 or more fetuses and are at
extremely high risk for preterm birth, in-
creased neonatal mortality, and signifi-
cant long-term neurologic morbidity. To
enhance the chances of having 1 or 2
healthy newborns for women carrying 3
or more fetuses, selective reduction in le-
tal number is available but is often an un-
acceptable choice for couples who have
experienced infertility problems.18 Dur-
ing the next 25 years, with continued im-
provement in pregnancy rates and bet-
ter monitoring of ovulation induction,
the frequency of multiple pregnancies
with assisted reproductive techniques
should decline.

Until the 1990s, few options were
available for treating male infertility.
However, a form of IVF that involves intracytoplasmic sperm injection (into
the ovum) is now a powerful tool for
achieving pregnancy in couples in
which men have low sperm counts or
high percentages of abnormal sperm.19
Another major advance involves cryo-
preservation of sperm and embryos, and
cryopreservation of ova or ovarian tis-
sue may become feasible. This tech-
nique should be of potential usefulness
in preserving fertility in women
undergoing chemotherapy for malign-
ancy and raises the possibility that, by
reimplantation of previously har-
vested and cryopreserved ovarian tis-
sue, women could “delay” menopause
for many years.

Contraception and Abortion. In de-
veloped countries, safe, voluntary con-
tral of fertility is now nearly universally available. Low-dose contraceptives
are safer than the earlier high-dose for-
mulations and have reduced adverse ef-
ffects. However, litigation or fear of liti-
gation have substantially reduced the
contraceptive options for US women by
effectively removing IUDs and most
long-acting hormonal contraceptives
from the market.13 Medical pregnancy
termination (methotrexate and mile-
pristine) appears feasible and safe but
is not widely available.20 Similarly, the
“morning-after pill,” administered af-
ter intercourse, is effective in reduc-
ong unintended pregnancies but is not
widely used. During the next 25 years,
many of these methods will become
more widely available. New formul-
tions of hormonal contraceptives, es-
specially the long-acting variety, will be-
come available, and additional barrier
or spermicidal types of contraception
will be introduced. Other approaches
may include immunologic suppress-
ion of ovulation.

Birth Outcomes
As maternal mortality declined in in-
dustrialized countries, greater empha-
is has been placed on fetal and neo-
natal survival and on improvement in
long-term neurologic outcomes, in-
cluding a reduction in cerebral palsy,
mental retardation, blindness, deaf-
ness, and hydrocephalus. Obstetri-
cians and neonatologists also began to
appreciate that the events leading to
these adverse outcomes often spanned
both the fetal and neonatal periods and
that further improvements in out-
come will require attention to the con-
Congenital Anomalies and Genetics. In the last several decades, the understanding of congenital diseases and structural anomalies has improved. For example, 1 in 1000 newborns has a neural tube defect, and the demonstration that as many as three fourths of these defects, as well as other congenital anomalies, are related to folic acid deficiency and are preventable by preconceptional folic acid supplementation presents an exciting opportunity to improve pregnancy outcomes.21 Vaccination for rubella has virtually eliminated congenital rubella syndrome and serves as a model for eliminating perinatal morbidity and mortality associated with maternal infections, such as varicella or parvovirus.

With increasing knowledge of the human genome and its products, the risk of a number of congenital diseases, such as cystic fibrosis, various hemoglobinopathies, and Tay-Sachs disease, can be predicted. Cytogenetic, biochemical, and ultrasound testing before midpregnancy can identify many other abnormalities, thus allowing parents to choose termination or, rarely, undergo “maternal-fetal surgery” to repair an anomaly with the fetus remaining in utero.22 While a wide variety of genetic disorders are now predictable, treatment options are rarely available, although many congenital defects might be treatable with gene therapy. For example, the congenital hemoglobinopathies and cystic fibrosis may be among the first disorders treated by this technique. For other congenital defects, options prior to pregnancy include a gamete donor for 1 or both affected parents or, once pregnancy is underway, selective termination of affected fetuses. Another technology, preimplantation diagnosis, involves DNA analysis of a single cell from a 4- to 8-cell embryo created by IVF.23 Implantation is performed only for nonaffected embryos.

In the future, use of microchip technology will allow rapid assessment of a large number of genetic variations in these single cells or in any cells derived from the parents or fetus. The next 25 years will see extensive improvement in the ability to screen for diseases, both preconceptionally and during pregnancy. Advances in therapy will lag behind, creating dilemmas about which patients and in what conditions to screen, and what to do with the information obtained.

Preterm Birth. In developed countries, preterm birth is the major cause of poor birth outcomes. In the United States in the last 2 decades, despite increasing availability of prenatal care, nutrition supplementation programs, and drugs to stop preterm contractions, the preterm birth rate has increased from 9.5% in 1980 to 11% in 1998.24 Part of this increase is due to multiple births associated with infertility treatments, but many preterm births occur spontaneously. None of the medical or public health strategies used to reduce preterm birth has succeeded.25 One of the major unsolved issues is the very high occurrence of preterm births among black women in the United States, who have twice the rate of preterm birth of other women, along with a 3- to 4-fold increase in the earliest preterm births, which account for most of the neonatal deaths and long-term morbidity.26 The increased rate of preterm birth accounts for much of the black-white difference in infant mortality (estimated at 6.3 deaths per 1000 live births for white women vs 15.1 per 1000 live births for black women in 1995).26

Perhaps the most important research finding in relationship to preterm birth is that many of these births are caused by intrauterine infection.27 Nearly 85% of the earliest preterm births are associated with an intrauterine infection prior to membrane rupture.27 The responsible organisms (eg, Ureaplasma urealyticum, Mycoplasma, Bacteroides, and Gardnerella) originate in the vagina and are not particularly virulent, so that intrauterine infection may remain quiescent for weeks or longer. The molecular pathways leading from infection to preterm birth are becoming better understood (FIGURE), and a variety of interventions to reduce preterm birth, including various antibiotic treatment strategies, suggest that some preterm births can be prevented.28 Research to prevent preterm birth will focus on strategies to reduce the intrauterine infections associated with preterm birth, along with strategies that interrupt the cascade of events leading to cervical softening and dilation, contractions, and spontaneous rupture of the membranes. Cytokines, prostaglandins, and metalloproteases all play important roles in preterm birth, and successful interventions will not only have to eliminate the intrauterine infections that initiate the production of these effectors, but also counteract their actions.

Another unsolved obstetric problem is that of poor uterine and placental blood flow associated with increased vascular reactivity and coagulation. Fetal growth restriction, preeclampsia, stillbirth, and infant neurologic damage are associated with maternal and fetal vascular and coagulation abnormalities.29 The pathophysiology of these disorders is becoming better understood, including the role of abnormal placenta tion, altered vascular reactivity, and the effects of various vasopressors, nitric oxide, and prostaglandins on the uterine and systemic vasculature. However, prenatal prevention strategies for preeclampsia, growth restriction, and fetal neurologic damage have not been effective. Future research efforts will better define the biological events leading to these vascular abnormalities and, based on these findings, appropriate interventions will be designed to prevent or treat the vasospasm and coagulopathies that diminish blood flow and ultimately reduce oxygenation and nutrition of the fetus.

Improving Newborn Outcomes. Since there has been limited success in reducing preterm births, keeping preterm newborns alive and healthy is a major priority. Although survival of preterm infants (especially those infants born weighing less than 1 kg) has increased markedly in the last 25 years, the absolute number of neurologically damaged infants who survive also has increased. In a study of 1151 infants with birth weight less than 1 kg who were assessed at age 18 months, 49% had...
abnormal neurodevelopmental and sensory assessments, and 17% had cerebral palsy.30,31 More subtle learning and behavioral disabilities appear at school age and further increase the burden of adverse outcomes. Therefore, improvements in survival in the last 25 years have not been matched by optimal neurodevelopmental outcomes. Other major causes of infant mortality are congenital anomalies and relatively rare deaths of term infants from infection and birth asphyxia. Although cerebral palsy is common in preterm infants, most cases develop unexpectedly after term deliveries not associated with birth asphyxia,32 and the etiology of these cases remains undefined.

Neonatal Care. Neonatal-specific care has been available for about 50 years, and intensive care for sick term and preterm infants has been widely available in many developed countries for 30 years. The early increases in survival resulted from improvements in temperature control and nutrition and use of antibiotics for infections. Mechanical ventilation and continuous positive pressure ventilation has been in use since 1971, and ventilation techniques continue to be refined. Specific therapies to regulate patency of the ductus arteriosus (ie, indomethacin to close and prostaglandin to keep open) have improved outcomes. Surfactant therapy for respiratory distress syndrome was developed based on a clear understanding of the pathophysiology of the disease. Imaging techniques such as ultrasound and magnetic resonance imaging permitted better diagnosis of cerebral hemorrhage and white matter disease (periventricular leukomalacia).

Current Scientific Foundation
Most effective therapies have resulted from the application to the care of infants of physiological information about organ system development derived from animal models. This integration of physiological information into clinical practice has increased survival and decreased the incidence of birth weight–specific adverse events such as intraventricular hemorrhage. The pathophysiology of several of the diseases unique to newborn medicine, such as respiratory distress syndrome and patent ductus arteriosus, are now understood and specific prevention strategies or therapies have been developed. However, other common neonatal disorders, such as bronchopulmonary dysplasia, necrotizing enterocolitis, and most types of brain injury, are poorly understood and lack specific therapies. For example, neonatal brain injury such as intraventricular hemorrhage or periventricular leukomalacia correlates with adverse neurodevelopmental outcomes such as cerebral palsy. However, the correlations are not strong because of the plasticity of the developing brain and the environmental influences that alter outcomes. Furthermore, many neurologically damaged infants do not have abnormalities that are identifiable with currently available imaging techniques.

The use of glucocorticoids to improve neonatal outcome illustrates a number of important points. In the 1960s, glucocorticoids were found to improve preterm newborn lamb lung function when given to the pregnant sheep prior to delivery.33 Since 1972, randomized trials in humans have demonstrated that a single short course of glucocorticoids prior to preterm delivery reduced the newborn risk of respiratory distress syndrome and the incidence of intraventricular hemorrhage, periventricular leukomalacia, and mortality and likely improved long-term

Figure. Pathways Leading From Intrauterine Bacterial Infection to Preterm Delivery
neurological status. Because of concern about increasing maternal and newborn infections and the potential long-term impact of glucocorticoids on the child, this intervention was not widely used by US physicians was low but increased after a National Institutes of Health consensus conference on this topic in 1994. While the published randomized trials evaluated a single course of therapy just prior to delivery, in practice in many locations, pregnant women risk for a preterm birth are given glucocorticoids for weeks. Animal studies and anecdotal reports in humans indicate that prolonged prenatal exposure to glucocorticoids decreases fetal growth and may also impair neurologic development. Therefore, for preterm human fetuses, a short course of glucocorticoids matures some fetal tissues and reduces adverse outcomes, such as respiratory distress syndrome and intraventricular hemorrhage, whereas prolonged administration impairs growth and possibly neurologic development. Timing of treatment in relationship to gestational age, dosage, and duration must be carefully considered to avoid permanent damage while achieving short-term benefits.

For infants already born, therapies that improve a primary outcome also may be accompanied by long-term collateral damage. Glucocorticoids, which have been used for the treatment of chronic lung disease in newborns, may cause neurodevelopmental deficits and adverse effects, such as hypertension, in later life. Progress will be slow if therapies must await long-term neurologic outcomes to validate safety. Therefore, surrogate markers for adverse long-term outcomes are needed. Neuroimaging is 1 approach but must be validated against important outcome measures. Separate from the effect of therapies, the size of the infant at birth predicts various adult diseases such as diabetes and hypertension. Better understanding of these relationships, their underlying biological mechanisms, and the effects of interventions will be a major focus of research in the next 25 years.

In contradistinction to the extensive studies on the use of glucocorticoids prenatally, other aspects of the care of fetuses and newborns have not been validated. On the other hand, the pioneering work by Sinclair and Bracken to promote research-based care is perhaps as strong in perinatal medicine as in any branch of medicine. The Cochrane Collaboration provides continually updated analyses of clinical trials. Several clinical research networks maintain large databases that provide accurate assessments of outcomes and also sponsor multicenter trials of new therapies. The neonatal databases demonstrate striking variation in disease frequencies and outcomes in different units, and the causes of these differences are being explored and used to generate hypotheses about components of care that may alter outcomes.

Cutting-Edge Research Activities

Understanding organ system development will permit identification of the factors that interfere with normal development and that can be targeted for therapies. Such a conceptual framework was used to develop indomethacin to close the patent ductus arteriosis and surfactant therapy for respiratory distress syndrome. Bronchopulmonary dysplasia is common in very-low-birth-weight infants, and a major manifestation is arrest of lung development with decreased septation and decreased microvascular development. Fibroblast growth factors 7 and 10 and thyroid transcription factor 1 have been identified as regulators of early lung organogenesis in mice by transgenic techniques. Other model systems using preterm and term animals are being used to explore how lung development is altered by lung injury. Long-term neurologic deficits are another adverse outcome in preterm newborns, and identifying factors that injure and protect the developing brain is crucial. Chronic chorioamnionitis, frequently associated with preterm births before 30 weeks’ gestation and with elevated proinflammatory cytokines in amniotic fluid, may be causal for intraventricular hemorrhage, periventricular leukomalacia, and ultimately cerebral palsy. The inflammation presumably damages developing neurons and impairs normal brain development. This etiology also may apply to term infants who develop cerebral palsy because blood from such infants contains indicators of inflammation. Interventions such as increasing arterial partial pressure of carbon dioxide and inducing hypothermia may protect the brain from ongoing injury. Even after severe injury, the developing brain demonstrates striking plasticity, in that infants can develop deficit-free despite large lesions that would normally be associated with neurologic deficits in the mature brain. Studies of neural cell replacement offer hope for brain-injured infants. It is important to emphasize that, although survival rates have been strikingly improved, about 50% of surviving infants with birth weights less than 1 kg have permanent neurologic disabilities. Reduction in long-term neurologic damage associated with being born preterm may be the most important goal for preterm births.

Critical Elements Needed to Achieve the Next Advancements

Progress in understanding the molecular and cellular mechanisms of mammalian development will accelerate with the application of genomics and proteomics to developing systems and ultimately will result in new therapies. Biological questions for the future may well focus on whether strategies to mature the preterm fetus to enhance survival inevitably cause subsequent adverse outcomes. If so, it will not be sufficient to identify major regulators of normal development, but also necessary to devise the modulators that can improve that development. Most regulators of development and mediators of injury act locally on select cell populations in precise temporal and spatial relationships, and therapies will need to be targeted and specific to be effective. These therapeutic advances will re-
Research Opportunities and Forecast: Reproductive Health and Birth Outcomes

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be essential, and information as to how inflammation injures the brain and the lungs of the preterm infant will translate into specific therapies to mitigate those injuries.

New imagining technologies will identify developmental abnormalities (with the primary interest being the brain) and make it possible to discover their implications for neurodevelopmental outcomes and to provide testable hypotheses about how to minimize brain injury. Although new technologies will modestly decrease mortality at very early gestations, the major goal should be an improvement in neurodevelopmental outcomes, with a societal consensus about the limits of viability.

Clinical care will generally improve as factors associated with better outcomes are identified. High-quality epidemiologic and outcome data will permit the field to focus clinical and basic research on relevant questions. Multicenter randomized controlled trials will become the accepted standard because most advances will be incremental and because large numbers of patients are needed to test efficacy and safety of new therapies. The outlook for progress for the care of the preterm or sick term infant is bright because of the insights that will come from developmental biology.

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REFERENCES


quire new insights from developmental and cell biology and perhaps new gene therapy strategies.

Forecast of Major Advances in Perinatology

Developmental biology will identify the regulators of critical developmental processes that impact clinical neonatology, including modulators of vascular and alveolar development in the lung, neuronal and glial migration and synapse formation in the brain, renal tubular development, and gastrointestinal function. Insights into injury mechanisms in developing systems will


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