Invited Commentary: An Assessment of Maternal Intergenerational Factors in Pregnancy Outcome

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Two articles in this issue (1, 2) address an important but often-overlooked area of investigation: maternal intergenerational factors in reproductive problems, or "...those factors, conditions, exposures, and environments experienced by one generation that relate to the health, growth, and development of the next generation" (3, p. 27).

Coutinho et al. (1) linked infants' birth certificates to mothers' birth certificates in Illinois. They found a consistent decreasing trend in the proportion of infants with low birth weight (<2,500 g) by maternal birth weight for both whites and African Americans and, conversely, an increasing trend for mean infant birth weight. However, at some of the lowest levels of mother's birth weight, the proportions of infant low birth weight were not the highest, nor were infant mean birth weights the lowest. This pattern, in which the lowest-birth-weight mothers did not have the smallest infants, has been seen by other investigators (4–6). One possible explanation is that these mothers had been preterm but healthy and had not been in utero long enough to achieve their genetic potential for prenatal growth.

Coutinho et al.'s finding that mother's birth weight was more strongly associated with infant birth weight than was paternal birth weight (1) also sheds light on the relative contributions of genes and environment to low birth weight. In general, it appears, as Coutinho et al. also show, that maternal growth factors—birth weight and adult stature—have stronger relations with fetal growth than do paternal growth factors (7–9).

Further support for the greater importance of maternal factors comes from studies showing that fetal growth is most strongly related to the birth weights of relatives in the maternal line (10–13). Furthermore, the association of maternal grandmother's stature to grandchild's fetal growth in two studies (9, 14) indicates a multigenerational process.

Lumey and Stein (2) report the latest findings from the Dutch Famine Birth Cohort Study, which takes advantage of an unfortunate "natural experiment." In this paper, they identify the mother's own early gestational growth as a critical period for her future reproductive success. The expected between-sibling parity relations of birth weight were disrupted in infants born to mothers who had experienced intrauterine exposure to the famine during the first trimester of pregnancy. Because adequate nutrition was reestablished during the third trimester—the time of large body mass accumulation—these mothers had higher birth weights than those mothers exposed in the second and third trimesters. This finding of low correlations between birth weights of mothers and infants is consistent with studies of mothers who are twins. As a group, these mothers have babies as large as those of singleton mothers, even though twins are markedly small at birth (15, 16). The growth pattern of twins is similar to that of singletons until late in gestation. Thus, as in the Lumey and Stein study (2), it is the mother's early gestational growth retardation which seems to be related to later suboptimal reproductive outcomes.

UNFOLDING EVIDENCE FOR INTERGENERATIONAL FACTORS

These two papers are part of a 60-year-old body of literature documenting the importance of intergenerational factors in pregnancy outcomes. The earliest such study, a birth cohort analysis of mortality in Great Britain carried out by Kermack et al. (17) in the 1930s, found that age-specific standardized mortality ratios improved from one generation to the next. Relative mortality throughout the life span was related to
the decade of birth, but declines in infant mortality lagged behind reduced mortality at later ages. The authors concluded that 1) the health of adults was largely determined by their health as children and 2) infant mortality fell only when maternal health had improved.

The Kermack et al. study seems to have stimulated the socioeconomic and social mobility studies conducted in the 1950s by investigators in Aberdeen, Scotland (18–22), which found that low birth weight and perinatal mortality rates were related to the social class of both the infant’s father and the maternal grandfather. Perinatal mortality and low birth weight were inversely related to maternal stature within each class. Infants of women born into the lowest class who married men in the highest class (upwardly mobile women) had lower rates of low birth weight and perinatal mortality than did the babies of women who married within the lowest class. Upwardly mobile women tended to come from smaller families, were better educated, had higher-status occupations, and, perhaps most importantly, were taller. However, the perinatal mortality and low birth weight rates of babies born to these upwardly mobile women still exceeded those of babies whose mothers were born into and married into the highest class. These studies indicate that both the conditions under which a mother is born and grows up and the conditions under which her pregnancies occur are important determinants of her reproductive success. They also suggest that it takes more than one generation to equalize socioeconomic disparities.

The association between maternal tallness and favorable pregnancy outcome has long been recognized by clinicians and seems to be a constant phenomenon in all human groups. An individual’s height is the result of a lifetime of growth, including the prenatal phase (23). The importance of maternal prenatal growth was recognized by studies assessing the link between mother’s birth weight and infant prenatal growth, first documented almost 30 years ago by a study conducted in Oxford, England (24). This study compared birth weight distributions of mothers for three categories of infants: small for gestational age (SGA), appropriate for gestational age (AGA), and large for gestational age (LGA). In comparison with AGA mothers, the birth weight distribution among the SGA mothers was shifted downward, and that of the LGA mothers was shifted upward.

Subsequent research in various countries has shown an inverse association between mother’s birth weight and numerous infant outcomes, including low birth weight, very low birth weight (<1,500 g), moderately low birth weight (1,500–2,499 g), preterm delivery (<37 completed weeks of gestation), relative intrauterine growth (SGA, AGA, LGA), respiratory distress syndrome, infant mortality, and perinatal mortality (4, 5, 25–31). Maternal intrauterine growth retardation (SGA) is a risk factor for infant SGA (14, 32), but the importance of maternal preterm birth in subsequent reproduction is not as clear at this time (6, 9, 14, 29, 32). A number of studies using linear regression have found direct associations between mother’s birth weight and infant birth weight, with or without adjustment for other factors (4, 6, 9, 33, 34). Some of these studies did not include preterm or low birth weight infants or those who died, thus decreasing the strength of any associations by excluding some of the smallest and most preterm infants (29, 34). Two studies have found a direct association between mother’s birth weight and maternal weight gain during pregnancy, indicating that mother’s birth weight also has long-term physiologic consequences (4, 25). It seems clear that by the time a first pregnancy occurs, significant maternal risk factors have already been established (35–37). In summary, relative risks associated with low maternal birth weight for various suboptimal infant outcomes are approximately 2 (1, 14, 25–29)—of the same order of magnitude as maternal smoking during pregnancy (38, 39).

EXPLANATIONS FOR INTERGENERATIONAL FACTORS

Prenatal and postnatal growth are genetically influenced, but socioeconomic factors play a very important role in the expression of genetic potential (9, 23, 40–42). For example, both prenatal and postnatal growth have undergone rapid positive secular increases, even in affluent countries. Conversely, economically deteriorating populations have shown negative secular trends in growth (42–45). Finally, the intergenerational increase in stature from parents to offspring was directly related to the relative intrauterine growth of the offspring, and it occurred in all social classes (44). Such associations between maternal growth, socioeconomic factors, and birth outcome have been found for decades (46–49) and are a key to understanding the intergenerational phenomenon.

It has been proposed that the pathway for the intergenerational phenomenon on a population basis is the secular change in prenatal and postnatal growth. On an individual basis, it may not be maternal size per se that is important but the degree to which a mother has achieved her genetic potential for growth (42). Results from two studies support this possibility. Peruvian teenage mothers who exceeded their mothers’ statures had bigger babies than those who did not (50). British mothers whose stature equaled or exceeded that pre-

dicted from midparental height had bigger babies than mothers whose stature did not (unpublished data from the 1958 British birth cohort).

A biologically plausible, nongenetic mechanism which could account for the intergenerational phenomenon is suggested by both human and animal data, described more fully elsewhere (42). Briefly, poorly grown human infants have small organs, primarily because of a reduced cytoplasmic: nuclear ratio but also because of reduced cell number. Reduced cell size and/or cell number are both consistent with a nongenetic mechanism resulting in long-term physiologic consequences. It is difficult to determine which organs may be responsible, since most of the organs of the body, not just the ovary and uterus, are involved in sustaining a pregnancy. Long-term, continuous prenatal and postnatal malnutrition in rats over many generations produced decreased birth size and adult size, increased mortality, persistent decreases in the size of most organs, and behavioral deficits (51). Depending on when it was initiated, nutritional rehabilitation took more than one generation to normalize growth (52).

FUTURE DIRECTIONS FOR INTERGENERATIONAL RESEARCH

The two articles published in this issue of the Journal offer further support for the importance of maternal prenatal growth and birth weight for the health of infants, and add to a substantial body of literature on this topic. Findings from these two studies and their predecessors are remarkably consistent. The results from the Dutch Famine Birth Cohort Study (2) at first seem contradictory to those of the Norwegian study, which found no difference in perinatal mortality among infants born to 5-year cohorts of mothers born during and after World War II (53). This apparent contradiction may be related either to the use of 5-year birth cohorts or to the fact that Norway did not experience extreme wartime malnutrition, or both. In any event, the more recent Norwegian study which found an association between mother's birth weight and perinatal mortality provided direct evidence of the importance of maternal prenatal growth in infant outcome (31).

There are four promising directions for future intergenerational research. First, efforts should be directed toward further elucidation of the relative contributions of the various measures of parental prenatal and postnatal growth to later birth outcomes. A second goal would be to clarify the role of intergenerational factors in cyclic poor pregnancy outcomes, such as those experienced by African-American women relative to whites (1, 3, 25, 26, 30, 42, 54). Maternal birth weight distributions of African-American mothers are skewed downward in comparison with those of white mothers (25, 26). For some suboptimal birth outcomes, African-American mothers appear to be at higher risk at all levels of maternal birth weight (1, 25, 26). Disparities in birth outcomes occur even between highly educated African Americans and whites (55, 56). One explanation may be that during the periods of these studies, most African Americans with high educational or occupational status were probably the first in their families to reach those levels and thus, like the upwardly mobile women in the British studies (21, 22), still experienced some reproductive disadvantage.

A third direction for research would be to use the methodology of intergenerational research to elucidate links between poor pregnancy outcome and later socioeconomic disadvantage. For instance, the 23-year follow-up of the 1958 British National Birth Cohort found that a birth weight of <3,000 g was associated with long-term residence in substandard housing and with financial difficulties (57). In the United States, an analysis of the 1988 National Maternal and Infant Survey found that mother's birth weight was directly related to later educational attainment and was inversely related to the risk of being unmarried (25). Similarly, US infants with low birth weights were at increased risk for disadvantaged living conditions between the ages of 2 and 11 years. These conditions included living in a low-income family in crowded housing and having mothers who were more apt to be single, in poor health, and of low educational attainment (58). Thus, it seems that low birth weight infants tend to be born into and to grow up in poor, high-risk families, are subjected to continued deprivation during childhood, and at the time of pregnancy tend to be mothers at high risk for suboptimal pregnancy outcome. Escape from this cycle seems to relate to a family's efforts to foster child health and development (21, 22), which may be more apt to occur in a receptive social environment.

The fourth promising direction for intergenerational research is related to recent work documenting an inverse relation of birth weight and early growth to several nonreproductive adult diseases, including non-insulin-dependent diabetes mellitus, hypertension, and coronary disease (59). The research related to this so-called "fetal/infant origins hypothesis" has recently been reviewed (60); criticisms include a failure to control for social class, substantial loss to follow-up because of elapsed time between birth and the time of study, conflicting evidence, and the potential importance of factors intervening between birth and adulthood.

Notwithstanding these criticisms, it is likely that prenatal and postnatal growth are factors in several...
adult nonreproductive diseases. Stature has been shown to be inversely related to risk of coronary disease (61, 62) and glucose intolerance (63). Since stature itself is related to birth weight (23), it appears possible that coronary disease and adult-onset diabetes mellitus will prove to be related to birth weight. The importance of growth is further supported by the finding that adult mortality is inversely related to stature, independently of weight (64). Reports from the Dutch Famine Birth Cohort Study, including the Lumey and Stein report in this issue of the Journal (2), and studies of mothers who were twins (15, 16) indicate that an important time for optimal growth is the mother’s own early intrauterine life. In one study, twins were also shown to be at slightly lower risk for coronary disease mortality (65). Thus, intrauterine processes which relate to long-term effects on both female reproduction and coronary disease seem to pertain to early gestational growth and development (66).

Childhood growth, particularly stature at age 6 years, has been proposed as the best predictor of mortality among populations (67). Economists have suggested that stature is an excellent indicator of the standard of living of populations, and that child growth is a good indicator of economic development (45). The importance of the long-term secular increases in stature to the secular decreases in both mortality and chronic disease prevalence was proposed by Fogel (68). It seems that good growth means good health and good health means good growth, and it appears that the quality of growth is both a cause and a consequence of the health status of individuals and populations.

The link between maternal prenatal growth and pregnancy outcome shown in the two papers appearing in this issue of the Journal (1, 2) illustrates one possible pathway whereby maternal socioeconomic factors impact the health of infants. Clearly there are many determinants of pregnancy success or failure, but the significance of preconceptional and intergenerational factors persists after adjustment for important risk factors pertaining to the pregnancy itself. On the basis of existing evidence, there is no reason to expect that any one factor will have a very dramatic effect relative to pregnancy outcome; and unfortunately, there is evidence that advantaged living conditions may not quickly override intergenerational effects.

SUMMARY

The increasing evidence that both prenatal and postnatal growth are important in the development of reproductive and other adult health problems would seem to warrant an expanded view of maternal and child health. We need to recognize that each one of us is a pregnancy outcome. The associations between suboptimal growth and various health problems are probably similar manifestations of the same underlying processes. There is substantial evidence of the importance of growth to health from both human and animal studies, and the concept is biologically plausible. Further investigations—clinical, epidemiologic, and experimental—will be necessary to better determine this concept’s validity and relative importance.

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