Early determinants of cardiovascular disease: the role of early diet in later blood pressure control

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ABSTRACT
It is now widely accepted that a gross change in the maternal diet during pregnancy results in offspring with raised blood pressure. More recently, results from human intervention studies and a range of animal experiments have questioned this concept. It thus appears that, when blood pressure is measured directly or by telemetry, the extent to which blood pressure is raised is largely dependent on the magnitude of the postnatal catch-up growth. In addition, such effects can be lost when appropriate corrections are made for current body weight. Consequently, offspring born to nutritionally manipulated mothers can actually have a lower blood pressure than control group offspring. At the same time, studies of the offspring born to contemporary women in developed countries show very little, if any, effect of changes in maternal diet on blood pressure in the offspring when assessed during childhood. In small animal studies, at least, the cardiovascular outcomes linked to small size at birth can differ between the sexes, which may be related in part to differences in kidney function between males and females. With respect to large animal studies, significant effects on blood pressure are less apparent and may relate to the much slower onset of hypertension. The challenge is to use our increased knowledge of the critical windows in early development to optimize later health. One clear priority is the prevention of excess adiposity and to determine how epigenetic mechanisms may provide novel strategies in this regard.

INTRODUCTION
One of the primary motivations of research within the developmental origins of adult health and disease has come from studies using historical cohorts in which significant relations between birth and/or placental weights and blood pressure have been found in the adult offspring (1). These relations have been extended by studies based on more extreme changes in total food intake during pregnancy as a result of the substantial survival and nutritional challenges imposed during World War II, eg, during the Dutch famine (2) and the siege of Leningrad (3). It is not surprising that under such adverse environments long-term health outcomes, primarily related to size at birth, have been shown in several populations, although recently the effects of exposure during childhood and adolescence have been highlighted (4).

The extent to which current diets can result in offspring with raised adult blood pressure remains an area of controversy that is potentially compounded by the ongoing obesity epidemic. Therefore, it is perhaps not unexpected that exposure to a variety of contemporary dietary regimens and/or supplements during pregnancy have very little effect on blood pressure in the offspring of women who are of normal body weight (5, 6) and thus not experiencing additional lifestyle challenges comparable to those present during wartime. In contrast, however, accelerated postnatal growth, particularly after dietary supplementation, potentially has a much stronger effect on later blood pressure (7). This emphasizes the close relation of childhood growth, current body weight, and cardiovascular control (8). The same interaction appears to be the case in animal studies when all the available growth data are viewed in conjunction with robust, direct measurements of blood pressure (9). It is therefore crucial that studies aimed at investigating the potential effect of diet on later cardiovascular disease use appropriate dietary regimens through infancy and childhood and do not simply focus on dietary interventions targeted at undefined time points in pregnancy alone.

FETAL AND POSTNATAL DETERMINANTS OF LATER BLOOD PRESSURE
A reoccurring theme from a majority of animal nutritional models of the fetal programming of adult health and disease is that offspring born to nutritionally manipulated mothers are hypertensive (10). This adverse outcome was largely based on experimental studies in rats in which the measurement of blood pressure was made by using the tail-cuff technique, in conjunction with measurements from multiple offspring born to the same mother. Although both of these methods have been widely and repeatedly criticized (11–15), surprisingly there are recent publications in which these erroneous methodologies are still used (16, 17). It is

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essential that all individuals working and reviewing publications in the field are aware of the marked differences in blood pressure outcomes that are apparent between blood pressure measurements captured by using 24-h continuous recording by telemetry when compared with those inferred from single-time-point measurements involving the restraint and artificial heating required with the tail-cuff method (18). Indeed, the procedure of isolating an individual rodent alone in a cage can be sufficient to increase its blood pressure (19).

In addition, another major factor that determines long-term cardiovascular outcome is whether birth weight and current weight, together with postnatal growth, are taken into account. Indeed, when these factors are considered and blood pressure is measured by either an indwelling catheter or telemetry, it is the extent to which growth rate is promoted after birth, in conjunction with the timing of maternal and/or offspring dietary changes, that determines whether blood pressure is raised or unaffected (9, 20). Clearly, it is not maternal diet alone that is important.

MATERNAL FOOD INTAKE AND BLOOD PRESSURE IN THE OFFSPRING

Support for the hypothesis that changes in maternal diet per se may not have any adverse affect on blood pressure in the resulting offspring comes from studies utilizing the effect of global changes in maternal diet made either during gestation or limited to defined stages of pregnancy. In both sheep and rats, it is apparent that when the offspring are raised under standard conditions, ie, out to pasture in the case of sheep or in an environmentally neutral regimen and housed within a cage for rats, that blood pressure in the offspring is actually reduced in weight-matched offspring in which catch-up growth is not seen throughout the entire lactational period (21, 22). Indeed, even when raised under a markedly obeseogenic environment, offspring born to nutrient-restricted sheep show the same degree of hypertension as controls (23) (Figure 1), although they may be showing a moderately exacerbated response if their blood pressure was actually lower before the onset of obesity. In rats, the only macronutrient model that has shown offspring to be hypertensive (as measured by telemetry) used pronounced differences in fat intake based primarily on lard. In these studies, mothers fed a high-fat diet in pregnancy and lactation received 4-fold more fat than controls (ie, 5.3% corn oil compared with 25.7% lard) (24) and, not surprisingly, compensated for the high energy density of a lard-rich food by reducing total food intake, with energy intake remaining similar between groups. This type of dietary intervention is clearly outside even the most extreme range of fat intakes seen in humans in developed countries. Even with this very large difference in maternal fat intake, the effect on blood pressure is seen only in female offspring, occurs only after 6 mo of age, and is accompanied (or preceded) by increased body mass (24). Consequently, if current blood pressure is corrected for current body weight, any difference from that of controls disappears (Figure 2).

SEX SPECIFICITY OF BLOOD PRESSURE OUTCOMES?
The extent to which sex determines the magnitude of cardiovascular outcome in offspring born to nutritionally manipulated mothers remains an area of debate. Many studies reporting sex-specific effects have studied only one sex and, even so, the response may be compounded by differences in growth rate either pre- or postnatally (9, 25). This is particularly important when considering sex-related differences in small animals because of the markedly different rates of growth between males and females (24), which are not apparent in large mammals or humans (26). In addition, fat mass and composition (ie, brown compared with white adipose tissue characteristics) differ very early in life with sex in rodents (27), but not in larger mammals, whereas such differences are not seen until adulthood in humans (26). In addition, there are substantial differences in kidney function between adult males and females that may well affect later blood pressure control (9). The extent to which such effects may be set in early life will differ between species with kidney development occurring primarily after birth in rodents (22) compared with prenatally in large mammals, including humans (28).

One more extreme model of dietary manipulation that has attempted to determine the extent to which potential cardiovascular outcomes may be mediated by sex steroids is the intervention of uterine artery ligation (29). This procedure, when undertaken at day 14 of gestation in rodents (term = 20 d), can result in intrauterine growth retardation, although a recent meta-analysis of publications in which surgery was conducted at 17 d gestation in the rat actually showed no effect on birth weight (30). It is, therefore, possible that the negative outcome in terms of birth weight may reflect publication bias, together with the statistical error of pooling data from multiple offspring from each mother (31, 32). Notwithstanding this, and irrespective of sex, it appears that the offspring born to dams subject to uterine artery ligation show catch-up growth, so that by 16 wk of age their body weights are at least the same as (if not greater than) controls (31, 32). This adaptation may be biased in part by the additional procedure of reducing litter size to 8 pups in all groups as this is known to preferentially promote postnatal growth (33), an adaptation that may be amplified in small offspring. Interestingly, in the model of maternal uterine artery ligation, sex hormones have opposite effects on blood pressure control, with gonadectomy (in males) at 10 wk of age resulting in a lowering of blood pressure after 12 wk of age (32), which is not seen in the offspring born to sham-operated mothers (31). In contrast, in females the difference in blood pressure seen in previously growth-restricted offspring persists
after ovariectomy (at 10 wk of age), and there is no difference in blood pressure reduction after estrogen replacement at 14 wk of age between groups.

The comparatively rapid responses to removal of sex steroids outlined above must, however, be viewed in the context of the large and varied number of effects these hormones elicit on metabolic regulation (34). For example, sex steroids can have profound effects on both body composition and food intake in the adult, even after only 2 wk of modulation (35). It would therefore be important to know whether these aspects of adult physiology were differentially affected by uterine artery ligation and subsequent catch-up growth. These factors may be particularly important in regulating blood pressure control over a 24-h period. Such information is essential in dissecting out the mechanisms by which the in utero environment can result in either increased or decreased blood pressure in the resulting offspring.

**EARLY NUTRITIONAL AND METABOLIC ENVIRONMENT AND CONFOUNDING EFFECTS ON BLOOD PRESSURE CONTROL IN OFFSPRING**

In large animal studies, however, removal of sex hormones results in appreciable differences in blood pressure between the sexes (36), which are not normally seen (37). Sex hormones therefore may be important factors in contributing to the unique differences seen between male and female offspring after exposure to very high levels of maternal glucocorticoids early in pregnancy (36). Further support to the proposal that sex-specific differences are seen only under extreme cases of endocrine manipulation is provided by the suggestion that, when embryos from sheep chronically exposed to a B vitamin- and methionine-deficient diet are transferred to mothers of normal nutritional status, hypertensive male, but not female, offspring can result (38). Comparison of the blood pressure reported in all of these animals that underwent embryo transfer with a comparable group (with respect to age and body weight) of control offspring born to naturally mated offspring shows that they are all hypertensive and that this effect is greater in females than in males (Figure 3). Thus, it is not unexpected that females are unresponsive under these nonphysiologic conditions. Indeed, the reported blood pressures in embryo-transfer offspring are equivalent to those found in markedly obese sheep (23) (Figure 1). In addition, the relative influence of the postnatal diet cannot be determined because all offspring exposed as embryos to a B vitamin- and methionine-deficient diet showed accelerated postnatal growth up to the time of weaning (38).

Indeed, one of the most plausible explanations for a resetting of cardiovascular control after exposure to nutrient restriction in utero resides within centrally, rather than peripherally, mediated adaptations (40). Thus, an increased expression of the angiotensin I receptor

![Figure 2](https://academic.oup.com/ajcn/article-abstract/89/5/1518S/4596907)

**FIGURE 2.** Summary of the effect of being born to rat mothers that consumed a diet containing 5.3% corn oil as compared with 25.7% lard during pregnancy and lactation on (A) adult body weight, (B) blood pressure, and (C) blood pressure corrected for body weight. Adapted from Khan et al (24). *Significant differences between groups, \( P < 0.05 \).

![Figure 3](https://academic.oup.com/ajcn/article-abstract/89/5/1518S/4596907)

**FIGURE 3.** Comparison of blood pressure in adult male (aged 2–3 y) or female offspring (aged 1–2 y) of sheep that were either conceived naturally or female offspring (aged 1–2 y) of sheep that were either conceived naturally or as a result of embryo transfer. Adapted from Gopalakrishnan et al (39), Gardner et al (40), and Sinclair et al (38). **, ***Significant differences between groups, \( P < 0.01 \) and \( P < 0.001 \), respectively.
within the brain stem may act to reset cardiovascular responsiveness (41), thereby explaining the leftward shift of the baroreceptor curve (40), an established precursor of adult onset hypertension (42). The extent to which such an adaptation may be regulated by epigenetic changes remains to be established (43). It has recently been shown that pharmacologic changes in glucose can affect the epigenetic regulation of energy sensing in vitro (44), and one challenge is to elucidate the relevance of these mechanisms in vivo.

In conclusion, simply changing maternal diet in either a physiologic or a pharmacologic manner does not necessarily result in hypertensive offspring. Critical windows in development that may determine later blood pressure include embryo genesis and placentalation, although the extent to which postnatal growth is subsequently altered is likely to be pivotal in determining long-term outcomes. Ultimately, it is within this context of growth and development that the potential effect of sex as an additional contributing factor to later blood pressure regulation must be considered. (Other articles in this supplement to the Journal include references 45–52.)

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