Perspective

Effects of the Holocaust on the Physical Health of the Offspring of Survivors

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The effects of the Holocaust on the second and third generations of the offspring of survivors have been discussed extensively in the scientific literature in Israel and abroad, particularly with regard to behavioral and mental aspects [1,2]. However, very little is known about their physical health. This review examines the suggestion that pregnancy in times of hunger and stress, which were an integral part of life during the Holocaust [3,4] and affected the health of the survivors, may also affect the health of their offspring not only in the immediate postnatal period but throughout their adult lives. Of particular interest is the possible emergence of medical problems, such as diabetes and cardiovascular and bone disease, later in life. Moreover, there are indications that this effect does not stop at first-generation offspring but continues to affect the second and third generations as well. It is therefore possible that the Holocaust scarred not just the millions of people who lived through it but its stigmata are passed on to their children and children's children.

The first to draw attention to a possible association between the weight and size of newborns and eventual morbidity was Barker and his co-workers who, in 1989, published several papers on the health of men and women who had been born in Hertfordshire between 1920 and 1930. They showed that cardiovascular morbidity, particularly death from ischemic heart disease, was inversely related to birth weight [5,6]. Leon and Ben Shlomo [7] reviewed the extensive scientific work on this relation that has been done since. Though several papers did not support it [8], and the research methods of some authors can be criticized [9], the existence of such a connection is acknowledged nowadays by most investigators, and recent studies fully substantiate it. Thus for example, Leon and co-workers [9,10], who surveyed the records of 15,000 men and women born at the University Hospital in Uppsala, Sweden, between 1915 and 1924 and followed until 1995 showed that mortality rates due to cardiovascular disease were inversely related to birth weight and Ponderal Index in both genders, though they were not statistically significant for women. Differences in socioeconomic conditions during pregnancy played no role. Risk factors for atherosclerosis were higher in low birth weight children. Lithell et al. [11] showed that the prevalence of type II diabetes in adults is inversely related to birth weight and

Ponderal Index, and that the lower the weight the higher the rates of diabetes 50 years later. Epidemiological studies provide ample evidence that low birth weight and hypertension are similarly connected [12]. Follow-up of children born during World War II in hunger-stricken areas corroborate this observation.

The Dutch famine

Most impressive epidemiological evidence comes from research on the Dutch Hunger Winter that lasted from November 1944 to April 1945. In September 1944 Dutch railroad workers went on strike. The Germans retaliated by blocking the movement of food, fuel and goods. The blockade of the canals was eased later, but the winter was harsh and the canals froze, so that effectively all transportation came to a standstill.

In order to guarantee the provision of basic dietary requirements and prevent severe hunger the Dutch government instituted food rationing. In October the allocation was 1400 kCal per day. In November it was 1000, and from December 1944 to April 1945, when Holland was liberated, it was 400–600 kCal. It should be noted that there was no shortage of food before the blockade and the hunger lasted only 6 months, unlike the hunger during the siege of Leningrad, not to mention years of severe hunger in the ghettos and concentration camps. The majority of the population had access to additional sources of food, such as church and public kitchens and the inevitable black market. Children and pregnant and breast-feeding women were allotted an additional 600 kCals per day. So it is reasonable to assume that the number of calories available was twice that quoted. This, too, is in contrast to the situation in the ghettos and concentration camps.

Government and public services continued to function throughout the winter, so the authorities were able to keep detailed and accurate records of demographic and medical data. This turned the Dutch Hunger Winter into a unique and unequaled research project that enabled examination of the immediate and long-term effects of food shortage on the health of the population.

One of the questions studied was the effect of prenatal maternal hunger on the offspring. The pregnancy period was divided into three trimesters of 13 weeks each, noting the severity of

hunger in each trimester. The records of 736 children born before, during and after the famine were examined. They contained data on the health, economic condition and social status of the mothers, on the course of pregnancy and weight changes during the pregnancy, as well as measurements of birth weight and length of the newborns and parameters like head circumference, head/body ratio, Ponderal Index, etc. [13]. Half of the women suffered from amenorrhea during the height of the hunger, a finding similar to the situation in the ghettos [3], and the number of pregnancies was reduced by 50%. Yet, the most striking findings were the birth weight which, although the hunger was short and not severe, was 9% less than before the hunger or in areas that were not under siege [13], and the increase in perinatal mortality.

Exposure to hunger or stress during the intrauterine period, conditions that were rampant during the Holocaust, may manifest in lower birth weight and length as well as other neonatal parameters

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The effect of hunger on the fetus depended on the trimester during which it took place. Under-nutrition during the first trimester of pregnancy had the greatest impact, resulting in increased weight of the mothers toward the end of the pregnancy, and in children with high birth weight who became overweight in adult life [14]. Mothers exposed to hunger during the second or third trimester had smaller children of low birth weight, decreased head circumference and small placental surface. Pregnancy during the siege was accompanied by a 4.3% weight loss on average. After the war, with food becoming abundant again, a weight gain of 10.5% was observed, average birth weight returned to its pre-siege level, head circumference increased by 2.5%, and body length increased by 1.5% [13].

A most interesting finding came up in an epidemiological survey of 300,000 new army recruits that was conducted in Holland in 1976. There was a significantly higher rate of obesity and hypertension among those who had been born 20 years earlier during the famine [6], and under-nutrition in the first trimester had the greatest effect on body weight [14,15]. Prenatal hunger, particularly in the first trimester, resulted in significantly more cardiovascular morbidity in later life, regardless of the weight at birth [16]. The lipid profile was atherogenic, with a low density lipoprotein/high density lipoprotein ratio as high as 14 (the desired ratio is < 3, and 11 is considered high risk), lower than normal apolipoprotein A and higher apolipoprotein B levels (although statistically non-significant). The weight of the mother before delivery did not affect the lipid profile [17]. Evidently, maternal under-nutrition, particularly during the first trimester of pregnancy, exposes the offspring to increased risk of cardiovascular morbidity in adult life.

Glucose intolerance was observed in 21% of adults whose mothers had a history of exposure to hunger during pregnancy. Levels of insulin and of blood glucose 2 hours after a 75 g glucose load were significantly higher if the exposure occurred during the last trimester [17]. There was no correlation between body mass index and glucose intolerance.

The effect of maternal hunger on the future health of the children was not limited to atheromatous lipid profile, glucose intolerance and cardiovascular disease. Maternal hunger during the first and second trimesters was associated with obstructive lung disease, and hunger in the third trimester was associated with an increase in restrictive disease. Also noted was a higher incidence of asthma [18].

Microalbuminuria was over three times more prevalent if the exposure to hunger was in the second trimester of pregnancy, and creatinine clearance was 10% lower [19]. This may be due to the fact that nearly 60% of the increase in the number of glomeruli occurs during weeks 18–32 of pregnancy. Animal experiments showed that one week of under-nutrition in mid-pregnancy results in significantly fewer glomeruli in the offspring and in eventual hypertension [19]. One may reasonably conclude that in mice and men exposure of the mother to hunger during a vulnerable time window can affect the development of the kidney and result in eventual ill health.

The Dutch famine undermined the mental health of the offspring as well. Much data have accumulated on the role of maternal hunger in the increased prevalence of mental illness, and of suicidal and antisocial behavior among the offspring [20,21].

As adults, those children will suffer from obesity, hyperlipidemia, hypertension, glucose intolerance and diabetes, and have higher rates of cardiovascular morbidity

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The siege of Leningrad

For obvious reasons the German siege of Leningrad (St Petersburg of today) during the Second World War is less extensively researched, but the available data present a picture similar to that of the Dutch famine. The city, with a population of 3,000,000 (including half a million children) was under siege for over 2½ years (8 September 1941 to 27 January 1943). More than 600,000 died, mostly from severe hunger [22]. Stanner and Yudkin [23] reported on the effects of the siege in 169 adults who had been born during the siege, compared with a control group of 192 adults born in Leningrad before the siege and 188 born outside Leningrad during the siege. Obesity and systolic hypertension were more common among those born in Leningrad during the siege.

Oddly, a comparison of people over age 50 who were born in Holland during the hunger winter with their Leningrad counterparts indicated that insulin resistance, glucose intolerance, atherogenic lipid profile and hypercoagulability were more common in the Dutch group. The same was true of hypertension, diabetes and cardiovascular disease [16,17,23]. This may be due to differences in the availability of food before and after the siege in Holland and Leningrad.

Animal research

Work with laboratory animals supports the epidemiological findings that maternal hunger during pregnancy affects the health of the offspring in later years and increases the incidence of obesity, glucose intolerance and hypertension [24-26]. Exposure of rat dams to hunger during pregnancy produced offspring of lower birth weight compared with controls. After weaning, the offspring were inclined to hyperphagia, and those fed a high calorie diet became obese, with systolic hypertension and hyperinsulinemia. This suggests that maternal malnutrition during pregnancy is the crux of obesity, hypertension and adult diabetes, the triad known as "Syndrome X" [27]. The scientific literature is rife with research papers that corroborate this connection [24,25].

Animal experiments show that those effects are not confined to first-generation offspring but may be propagated to subsequent generations

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Possible mechanisms

What is the connection linking maternal hunger during pregnancy, the birth weight of the offspring, and its future health? It is reasonable to assume that maternal under-nutrition coexists with fetal under-nutrition. When this occurs during critical stages of fetal development it may permanently affect the form and function of tissues and organs such as the endocrine pancreas, the liver and blood vessels [28]. Thus the environment of the fetus determines its development in the intrauterine period, its weight at birth, its postnatal growth and its future health. This is achieved through a process of "fetal programming," which aims to prepare the offspring for the postulated postnatal life [24,25]. This concept is widely accepted, particularly by Barker and colleagues [28], though not by all [29,30). However, the role of environmental and genetic factors in fetal programming is not yet clear.

Obstetricians prescribe dexamethasone, a corticosteroid, for high risk pregnancies in order to accelerate maturation of the fetal lung as a precautionary measure in case of premature birth. The result is smaller than average babies in every stage of the pregnancy, up to 160 g difference in weeks 30–32 [31].

Fetal cortisol level is lower than maternal cortisol levels, and is mostly produced by the fetus itself, though maternal steroids cross the placenta readily. In order to maintain the lower cortisol levels required for proper fetal development the placenta and the fetus itself have a "gate-keeper," 11 beta-hydroxysteroid dehydrogenase type 2 (11β-HSD2). This enzyme converts the maternal steroids to inactive metabolites rapidly, thus protecting the fetus from the harmful effect of high concentrations of the steroid (dexamethsone was selected as a therapeutic agent because it is not inactivated by the enzyme). Suppression of the enzyme in rat dams results in offspring with low birth weight, and with hypertension and diabetes in adulthood [32]. A low protein diet has the same effect. The embryos have low levels of 11β-HSD2 and are therefore exposed to high concentrations of maternal steroids. Exposure of the fetus to high concentration of corticosteroids – whether maternal (by suppressing 11β-HSD2) or by the administration of external steroids that are not inactivated by 11β-HSD2 (such as dexamethasone) – disrupts the hypothalamus-pituitary-adrenal axis [33] and results in an eventual rise in blood pressure and cardiac output and in suppression of lypolysis. A rise in fetal steroid levels, regardless of its source, will have the same effect. Maternal stress, causing a rise in maternal steroid levels, will determine the offspring's future response to stress [24]. The result is low weight at birth, and hypertension and diabetes in adult life [33].

Another factor that may play an important role in fetal programming is insulin-like growth factor-1 [34]. Fetal blood levels of IGF-1 are associated with blood pressure, with levels of fibrinogen and fasting blood glucose, and with bone density [24]. Steroids and IGF-1 do not cause a *genetic* change; they do not alter the DNA sequence in the gene. The change is *epigenetic*. It is achieved by modifying the expression of genes that encode the production of proteins and the activity of enzyme systems that control key processes [24]. This constitutes a rapid mechanism by which an organism can respond to environmental changes, so that a change in the expression of the gene that encodes cortisol receptors in the fetal brain will affect their number and sensitivity and thus modulate the function of the hypothalamus-pituitary-adrenal axis.

Evidently, low birth weight plays a significant role in infant mortality and in the emergence of chronic diseases in adult life. This may be due to suppression of the IGF-1 system in fetal life and to exposure to high levels of steroids. Retardation of intrauterine growth is associated with low levels of IGF-1 in umbilical cord blood [34]. The flooding of the fetus with maternal steroids due to low placental 11β-HSD2 has the same effect [35,36]. This range of processes that, acting during the intrauterine stage, plot the course of health and disease in the postnatal period and in adult life is the "fetal origin of adult disease" [37,38].

Fetal under-nutrition modulates the activity of enzymes that are involved in the control of carbohydrate metabolism and insulin resistance, slowing the development of muscle and adipose tissue and enabling the preferential channeling of nutrients to

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IGF-1 = insulin-like growth factor-1

the brain at the expense of other organs. This "brain-sparing effect" guarantees proper brain development during pregnancy even under adverse conditions. Retardation of the growth of other fetal organs *in utero* and the consequent lower requirement for food are thus part of the preparation of the fetus for the anticipated food shortage in the world outside the womb.

This predictive adaptive response may be the right solution for intrauterine hunger, but with a stiff price to be paid later. Insulin resistance is not limited to the prenatal period, it stays for life. A postnatal *milieu extérieur* with an abundance of food is the first step toward diabetes in later life.

What next?

The next question is whether or not the changes caused by severe under-nutrition during pregnancy are hereditary. It must be remembered that epigenetic information modulates gene expression without modifying actual DNA sequence. Nevertheless, epigenetic changes that take place during pregnancy or early on in the postnatal period may persist throughout life and be propagated to subsequent generations [26]. In essence, the question is: Will female offspring of hungry mothers who, as such, were adversely affected by intrauterine hunger (low birth weight, obesity, etc.) transfer those stigmata to their offspring. In other words, are the effects of maternal hunger limited to first-generation offspring, or can they be passed on to future descendants of well-fed mothers. Work by Stewart et al. [39] showed that birth weight of rat pups born to dams fed a low protein diet during pregnancy was significantly lower than that of a control group on regular chow, and the effect was further amplified in subsequent generations. Yet, resumption of a normal diet did not bring the birth weight of the low protein colony to normal for several generations. This experiment demonstrated that changes induced in the fetus by maternal hunger create a mechanism of fetal programming that is passed on to the offspring, though the environment no longer requires it. Similar results were shown by Pinto and co-workers [40].

The following scheme, by Drake and co-authors [26], attempts to illustrate the intergenerational effect of fetal programming: In the first round, harsh environmental conditions (e.g., hunger or stress) produce an offspring of low birth weight. Programming of cardiovascular metabolic and enzymatic pathways takes place during the pregnancy. In adult life this translates into increased cardiovascular risk (low birth weight increases the risk of death from heart disease threefold) as well as high-strung hypothalamus-pituitary-adrenal axis with exaggerated reaction to stress, which culminate in hypertension, insulin resistance and diabetes. In the second round, the fetus is exposed to an intrauterine environment with high levels of maternal cortisol and insulin, and to maternal hypertension. This forms the template that will be used by the process of fetal programming for the molding of a future adult along the same metabolic pathways as its mother. And so on down the line.

In summary, an inclement environment during crucial stages of fetal development (such as maternal hunger or stress-induced high levels of maternal steroids) manifests in low birth weight and programs the fetus in a way that exposes it to risks of increased cardiovascular morbidity and mortality in adult life. The epigenetic changes brought about by fetal programming are not limited to the fetal period. There is ample proof that they are permanent, last throughout life, and can be passed on to future generations.

Much is known about the mental health of the children of Holocaust survivors. However, in contrast to the extensive research done on the Dutch hunger winter and on the siege of Leningrad, to the best of our knowledge the effect of the Holocaust on the physical health of the offspring of the survivors has never been studied. It is high time this issue was dealt with.

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