Maternal Obesity Results in Offspring Prone to Metabolic Syndrome

Maria-Jesus Obregon

Instituto de Investigaciones Biomedicas, Consejo Superior de Investigaciones Cientificas y Universidad Autonoma de Madrid (CSIC-UAM), and Centro de Investigación Biomédica en Red de Fisiopatologia de la Obesidad y Nutricion (CIBERobn), Instituto de Salud Carlos III, Madrid, Spain

Obesity is reaching epidemic proportions in industrialized and developing countries. The main factors that determine the growing pandemic of obesity are changes in lifestyle leading to a reduced physical activity and increased sedentarism together with an increased rich-fat food intake. Obesity is a risk factor for many diseases such as type 2 diabetes, cardiovascular risk and stroke, hypercholesterolemias, as well as the incidence of several cancers.

Much discussion is still going on about the heritability of obesity, the influence of our genetic background *vs.* environment in the progression of obesity. Friedman (1) relates that the propensity to obesity (specifically our individual weight) is genetically determined as our height or our propensity for other conditions such as heart diseases or breast cancer. Others maintain that the environmental conditions, including sedentary habits, TV-watching, and high-fat diets are the main factors responsible for the increase of obesity during the last decades.

Most of us consider that increased food consumption and changes in lifestyle are responsible for the growing incidence of obesity in our society, but there is increasing evidence on the influence of prenatal events influencing the development of obesity during infancy and adulthood. Maternal environment especially during early fetal life seems to have a determinant role in the tendency to develop obesity of the progeny.

In the current issue of *Endocrinology*, the group of KH Moley (2) presents evidence on the influence of maternal obesity on the fetal and progeny outcomes, including adult life. The impact of maternal obesity starts in the reproductive tissues of the mother: the ovaries show increased apoptotic follicles, smaller oocyte size and number, and delayed meiotic maturation. The preimplantation events are also altered: IGF1R expression is blunted in the blastocysts, a fact that correlates to increased apoptosis (3). The IGF1R is critical for insulin signaling and glucose transport. Fetuses are smaller, and placental *igf2r* expression is increased. These events are accompanied by metabolic changes in 3-month-old adult mice with signs that resemble those of the metabolic syndrome: increased weight in mice born from obese mothers accompanied by glucose intolerance and higher cholesterol and body fat. Males are more affected than females.

From the above study we might only hypothesize that fat or high free fatty acids could be the nutritional signals that decrease IGF1R expression, but more research is needed in this subject. Besides, it is not clear the frontier between obesity and diabetic conditions, as 80% of the obesity conditions, including human obesity, are accompanied by insulin resistance. The literature on diabetes during pregnancy is extensive and will not be reviewed here (teratogenesis, altered organogenesis, macrosomy, predisposition for diabetes, and metabolic syndrome).

This study is relevant to facts occurring during human pregnancy. The offspring of obese women have an increased risk for obesity and diabetes. At birth they present higher percentage of body fat, higher insulin resistance, and higher leptin and IL-6 (4), suggesting that maternal obesity results in a higher risk for the progeny with metabolic insults already at birth. Therefore, the prevention of obesity during pregnancy should be a primary goal. Recent studies compare the outcome of children born from obese mothers before and after bariatric surgery (5). The

ISSN Print 0013-7227 ISSN Online 1945-7170
Printed in U.S.A.

doi: 10.1210/en.2010-0611 Received May 28, 2010. Accepted June 1, 2010.

For article see page 4039

children born after bariatric surgery, when the mothers have lost weight, had a lower prevalence of obesity than their siblings born from severely obese mothers before surgery. Those studies point to the importance and influence of the intrauterine environment on the future development of the children (6).

The studies on the cohort of people born from mothers pregnant during the big famine in World War II in The Netherlands led to the conclusion that prenatal famine exposure is associated with cardiovascular disease, type 2 diabetes, and decreased glucose tolerance in adulthood (7, 8). Poor nutrition *in utero* to the growing fetus may lead to permanent changes in insulin-glucose metabolism.

The observations derived from the Dutch famine cohort study (acute food restriction) and from obesity models (as the report by Jungheim *et al.* (2) in this issue and Refs. 6 and 7) seem contradictory, as both situations are diametrically opposite. But both conditions led to similar observations: increased incidence of diabetes and glucose intolerance, pointing to an exquisite regulation of the events occurring during fetal life. The fetal programming hypothesis suggests that the intrauterine conditions during certain periods of gestation may produce irreversible changes in certain metabolic functions, leading to diseases during adult life.

The intrauterine environment and nutritional conditions during fetal life may be considered as epigenetic mechanisms that could play a role in the development of obesity during adult life. The epigenetic modifications alter gene function (silencing or activating) without changes in DNA, are heritable, and are caused by environmental agents, including nutrition, pollutants, and other agents (9). We need more research on the specific events taking place in the case of obesity during pregnancy, such as DNA methylation or histone acetylation. Early overfeeding may be an epigenetic risk factor for the programming of the CNS mechanisms predisposing to augmented food intake (10). There are fascinating studies on the effects of maternal behavior (nurturing, licking, grooming) in the rat, inducing epigenetic changes in the glucocorticoid receptor gene promoter in the hippocampus (11), and those changes were associated with alterations in the response to stress of the litters and alterations in the hypothalamic-pituitary-adrenal axis.

Nutrition is one of the best candidates for epigenetic modifications in diabetes and obesity (12). This means that not only genetic factors or familiar environment contribute to the development of obesity in the progeny, but also the uterine environment seems to determine the obesity degree in the progeny born from obese mothers. The uterine environment seems even more important than genetic factors. Epigenetic mechanisms may be playing a role in the increasing prevalence of obesity.

Acknowledgments

Address all correspondence and requests for reprints to: Maria-Jesus Obregon, Ph.D., Instituto Investigaciones Biomédicas, Consejo Superior de Investigaciones Cientificas y Universidad Autonoma de Madrid (CSIC-UAM), Arturo Duperier, 4, 28029 Madrid, Spain. E-mail: mjobregon@iib.uam.es.

This work was supported by Research Grants SAF2009/09364 from Plan Nacional, Ministerio de Ciencia e Innovacion (MICINN). Centro de Investigación Biomédica en Red Fisiopatologia de la Obesidad y Nutricion (CIBERobn) is an initiative of Instituto de Salud Carlos III (ISCIII), Spain.

Disclosure Summary: The author has nothing to declare.

References

1. **Friedman JM** 2004 Modern science versus the stigma of obesity. Nat Med 10:563–569
2. **Jungheim ES, Schoeller, EL, Marquard KL, Louden ED, Schaffer JE, Moley KH** 2010 Diet-induced obesity model: abnormal oocytes and persistent growth abnormalities in the offspring. Endocrinology 151:4039–4046
3. **Chi MM, Schlein AL, Moley KH** 2000 High insulin-like growth factor 1 (IGF-1) and insulin concentrations trigger apoptosis in the mouse blastocyst via down-regulation of the IGF-1 receptor. Endocrinology 141:4784–4792
4. **Catalano PM, Presley L, Minium J, Hauguel-de Mouzon S** 2009 Fetuses of obese mothers develop insulin resistance in utero. Diabetes Care 32:1076–1080
5. **Smith J, Cianflone K, Biron S, Hould FS, Lebel S, Marceau S, Lescelleur O, Biertho L, Simard S, Kral JG, Marceau P** 2009 Effects of maternal surgical weight loss in mothers on intergenerational transmission of obesity. J Clin Endocrinol Metab 94:4275–4283
6. **Godfrey KM** 1998 Maternal regulation of fetal development and health in adult life. Eur J Obstet Gynecol Reprod Biol 78:141–150
7. **Roseboom T, de Rooij S, Painter R** 2006 The Dutch famine and its long-term consequences for adult health. Early Hum Dev 82:485–491
8. **Ravelli AC, van der Meulen JH, Michels RP, Osmond C, Barker DJ, Hales CN, Bleker OP** 1998 Glucose tolerance in adults after prenatal exposure to famine. Lancet 351:173–177
9. **Yajnik CS, Godbole K, Otiv SR, Lubree HG** 2007 Fetal programming of type 2 diabetes: is sex important? Diabetes Care 30:2754–2755
10. **Chen H, Simar D, Morris MJ** 2009 Hypothalamic neuroendocrine circuitry is programmed by maternal obesity: interaction with postnatal nutritional environment. PLoS One 4:e6259
11. **Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, Dymov S, Szyf M, Meaney MJ** 2004 Epigenetic programming by maternal behavior. Nat Neurosci 7:847–854
12. **McCurdy CE, Bishop JM, Williams SM, Grayson BE, Smith MS, Friedman JE, Grove KL** 2009 Maternal high-fat diet triggers lipotoxicity in the fetal livers of nonhuman primates. J Clin Invest 119:323–335