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Transferred maternal fatty acids stimulate fetal adipogenesis and lead to neonatal and adult obesity

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A B S T R A C T

The prevalence of adult and childhood obesity are increasing. Most of the human newborn's body fat accumulates in the last half of intrauterine life. Fat in the fetus was thought to be mostly synthesized from glucose, but now it is commonly accepted that the bulk of it is the product of placental transfer of maternal fatty acids. Transported fatty acids originate in maternal plasma "free" fatty acids, fatty acids hydrolyzed from maternal plasma triglycerides, and the poly-unsaturated fatty acid component of maternal phospholipids. Glucose remains an important precursor of alpha-glycerol phosphate, to which most transported fatty acids are eventually esterified. Maternal plasma lipids are elevated in late pregnancy and even more in obese and diabetic pregnant women. This accelerates the placental transport of fatty acids. The hypothesis presented in this paper rests on the observations that the exponential increase in fat tissue in the human embryo's body occurs in time to parallel the increase of lipids in the mother's blood and depends on the chemical affinity of the transcription factor PPAR gamma to fatty acids and on fatty acid stimulation of adipocyte generation from precursor cells. The hypothesis asserts that transported maternal fatty acids activate the transcription factors in the fetus and initiate conversion of the mesenchymal stem cells into adipocytes. In obese and diabetic mothers, the higher plasma lipids facilitate increased placental fatty acid transfer. This will increase adipocyte generation and, through this, the prevalence of babies with increased fat cell size and number. Babies born with increased adipose tissue cellularity will have greater probability of growing up to become obese adolescents and adults. These newborns, whose obesity is hyperplastic as well as hypertrophic, as adults will have difficulty losing weight through diet and exercise or will regain the lost weight more quickly than others without these characteristics. Accordingly, increased placental fatty acid transfer and accelerated adipocyte generation may explain not only neonatal obesity, but some aspects of the adult obesity epidemic also. It is therefore recommended that prevention of fetal fat cell hyperplasia, by lowering maternal plasma lipids in mid and late pregnancy, should be attempted in pregnancies at risk for macrosomia.

Background

Prevalence of obesity

Overweight/obesity (the two differ only by degree of excess adipose tissue) was probably the most common metabolic disease in developed countries in the first decade of the 21st century [1]. Its prevalence has reached epidemic proportions and shows little if any trend in diminishing in the second decade of the century [2]. It has a well-documented impact on public health by accelerating or complicating other illnesses, such as cardiac, vascular, neoplastic diseases and diabetes mellitus. It taxes the economy, as the above specified illnesses if complicated by obesity, show increased morbidity, mortality, absenteeism from work, medication demand, surgery, hospital admissions, and threats to quality of life [3]. Even more disturbing is, that though the prevalence of childhood obesity had been thought to have reached a plateau in some age groups [4], it was found recently to be universally increasing [5].

Etiologic factors in the causation of obesity

Innumerable etiological factors, some inherited, some acquired, some environmental, have been incriminated as potential causes of obesity. Listing (and referencing) all is beyond the scope of this paper, especially because in any individual case more than one of the potential causes may play a role. It is therefore sensible to consider the obesity-overweight condition a syndrome in which one or more of a multitude of etiologic factors may lead to a common phenotypic manifestation characterized by excessive adipose tissue development or accumulation. In this paper the term "adipose tissue" denotes subcutaneous and abdominal white adipose tissue. Brown and beige adipose tissue have different function, metabolism and probably even different genetic background, therefore these require separate discussion.

Morphological types of obesity

Increased adipose tissue mass is characterized by expanded fat cell size, which evolves from excessive deposition of fat into, or accelerated

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synthesis of fat in preexisting adipocytes (“hypertrophic” obesity), by excessive generation of new adipocytes (”hyperplastic” obesity) [6], or by a mixture of both hypertrophic and hyperplastic histological varieties. New adipocytes may emerge through differentiation from precursors (such as pluripotent mesenchymal stem cells) [7], or through division (multiplication) of existing fat cells. The altered energy balance that leads to obesity is summarized as greater intake (and storage), than expenditure of calories [8].

Adipose tissue after weight loss

Several approaches involving various diets, exercises, and a combination of thereof (life-style modification therapies) showed initial success in achieving significant weight loss. However, relapse rate was high in all long-term studies [9,10]. The cause for the high relapse rate is still debated, but some authors blame it on the “thrifty gene” (a term originally coined to explain diabetes mellitus and describes an inherited tendency acquired by the hunter-gatherer early human ancestors), which supposedly facilitated storage of excess calories in times of plenty and decreased catabolism when food was scarce [11]. The “thrifty gene” hypothesis is often quoted, though not universally accepted [12]. Alternatively, failure to maintain weight loss is also blamed on the hypothalamic, thyroid, gastro-intestinal, gonadal and pituitary hormones [13,14] which may influence appetite and heat production, on cytokines [15], which may mediate the actions of these hormones and on the autonomic nervous system which may provide alternate pathways for the hypothalamic impulses [16]. Examination of adipose tissue histology of subjects after weight reduction yielded the surprising information, that weight loss mostly caused decrease of adipose cell size, but not reduction of adipose cell number [17,18]. This observation is compatible with the possibility that weight loss maintenance is difficult in a subset of obese subjects whose remaining excessive number of shrunken fat cells after a period of fasting may send quantitatively increased signals to the hypothalamus to increase their volume and thus to restore the perceived “correct” energy balance [8].

Peak periods of adipocyte differentiation

Studies in human subjects suggested that peak periods of adipocyte differentiation (recruitment from pluripotential precursor cells) takes place in the first two years of life and in the pre-pubertal years [6,19]. These statements were later questioned when other investigators found progressive increase in the number of adipocytes over the years of childhood and adolescence [20,21]. Contrary to both of these opinions (and much before either of them), Widdowson and Spray found very little (if any) fat in human embryos aborted in the first and second trimester and described almost exponential growth of fetal adipose tissue in those stillborn in the third trimester [22]. Fat content of the embryos increased from less than 1% to 15–28% of body weight in the last 3–4 months of pregnancy. A more recent study on appearance of lipids in tissue obtained from human abortion places the differentiation process earlier, from the 14-th to 24-th weeks of gestation [23]. In either case it is safe to state that the fastest period of adipocyte differentiation (recruitment) in the human life cycle must take place not in childhood, but during intrauterine life.

Signals initiating and regulating adipocyte differentiation

The signal that initiates adipocyte differentiation in the embryo has not yet been positively identified. Adipocyte differentiation can be induced in vitro by a variety of physical [24], nutritional [25], hormonal [26] influences, but mostly by transcriptional factors, such as the PPAR family of molecules (PPAR stands for peroxisome proliferation activating receptors) [27] acting on nuclear receptors. Which of these factors is responsible for the initial step in vivo, remains subject of debate. Among many “candidate” substances, saturated and more decisively, the polyunsaturated fatty acids have been mentioned as regulators of the differentiation process [28]. Arriving (mostly bypassing the liver through the Ductus Venosus) to the subcutaneous or to the abdominal fat cell precursors (pluripotential mesenchymal stem cells or specialized cells of the vascular epithelium), fetal plasma free fatty acids bind to fatty acid receptors [29,30], to fatty acid binding proteins [31,32] and subsequently to fatty acid transport proteins [33,34]. Most significantly fatty acids bind to transcription factors of the PPAR family [27,35,36]. This may be the decisive step toward differentiation, though other molecules, such as CCAAT-enhancer binding protein (CCAAT stands for cytosine-cytosine-adenosine-adenosine-thymidine) [37] and ADD1/SREBP1 (ADD stands for adipocyte determination and differentiation factor and SREBP stands for sterol regulator element binding protein) [38] also participate in the process. This cascade of events has been shown to operate in pre-adipocyte cell lines [39] bringing the in vitro observation nearer to the real life situation. Hormonal factors, such as glucocorticoids [40], insulin [26], thyroid hormones [41], leptin [42], adiponectin [43], placental hormones [44], growth hormone [45], insulin-like growth factor 1 (IGF 1) [46] and others provide yet another layer of regulation, some positive, others in negative direction. Their actions vastly increase the complexity of adipogenesis and its regulation, beyond the scope of this paper.

De novo fat synthesis by adipocytes and precursors: the Pedersen Hypothesis

Newly differentiated fat cell precursors do not contain significant amounts of fat. Triglyceride accumulates later into cytoplasmic vacuoles which coalesce into a large blob, all but squeezing out the cytosol and even pushing the nucleus to the periphery of the cell. For the past 60 years, based on Pedersen’s work on babies born to diabetic mothers [47], it was thought that fetal fat is derived from maternal glucose, which passes the placenta easily (in diabetics more than normal quantities). According to the Pedersen Hypothesis, glucose stimulates the fetal islets to produce excess insulin in babies of diabetic mothers, causing hyperinsulinemia, which facilitates glucose entry into adipose tissue cells and causes neonatal obesity.

Fat transfer through the placenta: the original fatty acid hypothesis

Case reports of obese babies born to mothers who showed no evidence of diabetes but who later (sometimes several years after termination of their pregnancy) became diabetic raised doubts as to the validity of the Pedersen Hypothesis. Looking at alternate possibilities, my laboratory investigated the placental transfer of palmitic acid, a long chain fatty acid prominent in human plasma and in adipocyte triglycerides as well. We found significant transfer, using an in vitro perfusion system of freshly delivered whole placentas [48]. Subsequently, we showed brisk uptake and esterification of palmitate by incubated human placenta slices [49]. As the fat content of the placenta is low [22], our finding suggested a transfer mechanism requiring transient passage through the intracellular compartment. We then hypothesized that transferred maternal fatty acids may significantly contribute to fetal lipogenesis [50] and therefore to the obesity of babies born to diabetic mothers. In the present paper the term “fatty acids” denotes long chain fatty acids, with 16 to 22 carbon chain length. The term “free fatty acids” denotes long chain fatty acids loosely complexed to plasma albumins. This term is preferentially used in the North American medical literature over the chemically more correct term “non-esterified fatty acids” or “NEFA”.

Origin of the transferred fat

Intact triglycerides cannot cross the placenta. In contrast, we showed that fatty acids are readily transferred through this organ (tissue). Transfer from maternal “free” (i.e. albumin complexed) fatty

acids was supported by reports of elevation of plasma free fatty acids in pregnancy (especially in the last trimester) [51] and elevation of free fatty acids of pregnant gestational diabetic women over and above that seen in the general (non-diabetic) pregnant population [52,53].

Maternal plasma triglycerides and the role of placental lipases

Evidence for the presence of enzymes in the placenta, which split fatty acids from circulating maternal triglycerides and phospholipids (lipoprotein lipases, placental lipases and phospholipases) [54,55] emerged and gained importance when increased maternal plasma triglycerides in the third trimester (and even higher levels of triglycerides in pregnant diabetic mothers) were reported [56,57]. This opened up the possibility that most maternal plasma lipid fractions which contain fatty acids in esterified or in non-esterified form can serve as substrates for placental transfer.

Plasma lipids in pregnancies complicated by obesity and gestational diabetes

Two maternal disease states, diabetes type 2 (including gestational diabetes and pre-diabetes) and obesity, were reported to show statistical association with obese newborns [47,58]. Interestingly, both are also known to be associated with elevated maternal plasma lipids [56,59].

Based on the information discussed in paragraphs “a” to “k” a unified concept emerged regarding the origin and persistence of fetal fat. This is summarized in the following hypothesis.

The expanded fatty acid hypothesis

1. Fatty acids transferred from mother to the fetus serve dual roles: in addition to providing the bulk of the fat deposited into adipocytes, fatty acids may also be factors in initiating recruitment and differentiation of adipocytes.
2. The transferred fatty acids are derived from several lipoprotein fractions of the maternal plasma. These fractions include “free” fatty acids (complexed to albumin), or from lipids bound to and enveloped in protein as low density (LDL) and very low density (VLDL) lipoprotein triglycerides, chylomicron triglycerides, cholesterol esters and phospholipids.
3. Maternal fatty acids are released from the parent compounds by placental enzymes (lipoprotein lipase, placental lipase and phospholipases) to render them available for the placental transport processes.
4. Polyunsaturated fatty acids may serve several complex roles in the fetus, among them the regulation (stimulation and/or inhibition) of adipocyte differentiation.
5. Excessive fatty acid transfer across the placenta may be the common pathway by which diabetic (Type 2, gestational and pre-diabetic) and non-diabetic obese (overweight) mothers develop obese fetuses. High maternal lipid levels in these conditions increase the mother-to-fetus gradient and facilitate fatty acid transfer to the embryo.
6. Glucose is probably the sole calorigenic nutrient in the early phase of human embryogenesis and insulin-driven glucose metabolism remains throughout pregnancy, the major source of glycero-phosphate to which fatty acids are esterified in fetal adipose tissue.
7. Obese newborns have enlarged fat cell size and probably also more numerous fat cells than normal weight neonates. Accordingly, they have hypertrophic as well as hyperplastic obesity.
8. Babies born with excessive adipose tissue are more likely to grow up to be obese adolescents and adults. One reason for this may be that diet and exercise will not reduce their excessive fat cell numbers, even though it may lower adipocyte volume. The remaining excessive number of adipocytes, shrunken because of loss of fat content, will signal (via hormonal or neural route) to the hypothalamus to restore their volume. Hypothalamic and other neural centers will then elicit increased appetite, decreased heat production or both, to regain the lost weight, preserve calories, and to restore the previously established “status quo” of cell volume and cell membrane tension.
9. The second half of gestation would yield an uncommon opportunity to prevent fetal adipocyte generation. As the time period required for maternal life style modification to prevent excess fetal adiposity is finite and short, it is conducive to inspire adherence to intensive diet and exercise programs otherwise doomed to failure.

Discussion

The hypothesis outlined above connects maternal hyperlipemia and exaggerated fatty acid transfer across the placenta to adipocyte hypertrophy and hyperplasia in the fetus, and subsequently, to adult obesity. It touches upon the immensely complex process of intrauterine development and seeks to explain with a single common pathway the high prevalence of excessive weight of babies born to obese and to hyperglycemic mothers. It does not assign exclusive role to fatty acid transport but emphasizes the importance of the formerly minimized role of the fatty acids, especially in the second half of the pregnancy.

The groundbreaking work of Widdowson and Spray [22] drew early attention to fetal metabolism, but it was Jørgen Pedersen, a Danish pediatrician and epidemiologist, who not only recognized the macrosomia and excessive fat depots of babies born to diabetic mothers [47], but also formulated a logical, cohesive hypothesis to explain this anomaly. His hypothesis that placental glucose transfer, excessive in hyperglycemic mothers, leads to fetal islet stimulation which results in hyperinsulinemia that in turn leads to excessive de novo fat synthesis provided seemingly logical explanation for the obesity of babies of diabetic mothers and remained unchallenged for several decades. Indeed, glucose and insulin are still considered to be the major metabolic forces leading to adipogenesis in the fetus in the first and for most of the second trimester of pregnancy. Fetal insulin may even be an early initiator of adipocyte recruitment and differentiation [26].

Transfer of fatty acids across the perfused human term placenta was observed in and reported by my laboratory almost 50 years ago [48] and its role in the causation of obesity in newborns of diabetic mothers was suggested shortly thereafter [50]. Independent confirmation of placental fatty acid transfer using a different experimental methodology was published [60] shortly thereafter. While the authors of that paper attributed smaller quantitative significance to the fatty acid transfer, they unquestionably confirmed the transfer’s existence. Other investigators using isotope labelled fatty acids in vivo (oral doses given to pregnant women few hours before caesarian section) [61] and still others measuring umbilical cord vein-artery fatty acid differences also supported our findings by showing placental fat transfer and fetal fat extraction [62,63]. Indirect support for placental fat transfer also came from identification of microsomal and lysosomal enzymes in triacyl glycerol metabolism [64] in the placenta and from characterization of fatty acid transporters and binding proteins in placentae [65]. Maternal plasma lipid concentrations are elevated in the third trimester of pregnancy [56,57]. Fatty acids released from triglycerides of plasma lipid fractions by placental lipases are important substrates for transfer to the fetus.

Polyunsaturated fatty acids, a heterogeneous class of molecules of which some may have varying (mostly stimulating, but some inhibiting) effects on adipocyte differentiation [28], have their own transport process. The unique configurations of members of this class of fatty acids and their special roles makes it understandable that individual transport processes developed in placental tissues to ensure availability of adequate quantities of these substances for use by the fetus [66,67]. Blood levels of polyunsaturated phospholipids are low in gestational diabetic women [68]. The significance of this observation is unclear.

Differentiation of adipocytes from their precursors has received

much attention, but the initiator of the recruitment and of the differentiation process has not been identified with certainty. Genetic preprinting [69,70,27] probably precedes any hormone and substrate effects in the process. Hormone and substrate influences on adipogenesis may be simultaneous or even synergistic. Of the several hormones that participate in the process [71,26,14], insulin seems to be of particular interest, as this hormone appears early in endocrine cells of the developing embryo [72–74]. Of the candidate substrates, glucose is likely to precede fatty acids in early development because its transfer across the maternal-fetal barriers may require less elaborate mechanisms. However, from mid-term pregnancy to the birth of the baby, fatty acids gain more importance as they deliver the bulk of what becomes the subcutaneous and abdominal fat of the newborn. Fatty acids are attractive candidates for having decisive roles in adipocyte generation in the second half of the pregnancy because of their chemical affinity to the PPAR gamma molecule [75,76], which is a key regulator of the transcription mechanism driving cell differentiation and because of the simultaneous rise of fatty acid concentration in the maternal plasma [51–53] with their almost exponential increase in fetal fat depots [22]. While this temporal association between the rise of maternal plasma lipids and accumulation of fetal fat depots does not prove cause and effect relationship, it certainly gives reason to consider it and to further explore this possibility.

Adipose tissue is not a homogeneous entity. Heterogeneity of adipose tissue is revealed by developmental, morphological and functional differences seen in white, brown, and beige adipose tissues [77], and observed in the chronology of white adipose tissue appearing in different body parts [23]. Differences in cell size characteristic to each location and possibly differences in function also show heterogeneity [78]. The present hypothesis is focused on white subcutaneous and abdominal adipocyte metabolism, though the other, metabolically active cell varieties undoubtedly play important roles in adaptation to starvation and regrowth.

Statistical and epidemiological observations showed direct correlation of adult obesity with childhood and neonatal obesity. Those born with excess adipose tissue have two to four times higher probability to grow up to become obese adults than those born with normal weight [79,80]. A recent computer simulation model predicted the persistence of childhood obesity into adulthood, resulting in obesity in more than 50% at age 35 [81].

Gestational diabetes mellitus is not the only maternal condition associated with both neonatal obesity and with high maternal plasma lipid levels. Maternal obesity is also associated with high maternal plasma triglycerides [59] and with high prevalence of excessive birth weight and fat depots of the newborns [58,82].

Excessive fetal adiposity is not a necessary consequence of elevated maternal plasma lipids. The association of maternal plasma lipids and fetal obesity is complex and other factors, (placental vasculature, placenta size, maternal circulation and others) may introduce modifiers into the equation. For example, maternal hypertension and preeclampsia correlate with high plasma lipids [83,84], but not with obese or large for gestational age babies [85]. The dissociation between maternal lipid levels and fetal weight may be related to the decreased size of the placenta and to vascular lesions observed in the placentae of hypertensive and in preeclamptic women [86].

Two additional maternal subgroups require further explanations because they show seemingly divergent response to insulin therapy of their underlying diabetic states. These two conditions are a) type 1 diabetes of pregnant women, which is always treated with mandatory insulin therapy, and b) gestational diabetes, (perhaps along with type 2 diabetes during pregnancy), which (as part of aggressive glycemic control programs) are also often treated with insulin therapy. It is common knowledge that insulin lowers blood sugar, but it is less widely known that insulin has a similar, perhaps even stronger effect on plasma free fatty acid concentrations [87]. Insulin effect of lowering plasma fatty acids is brisk and lasting [88–90]. Indeed, even endogenous insulin release after glucose infusion will result in sustained suppression of plasma free fatty acids [91]. Thus, if injected insulin in these two groups of patients simultaneously lowers plasma glucose and free fatty acid concentrations, it should result in lower rate of placental free fatty acid transport and therefore should decrease fetal fat accumulation also. Surprisingly, while babies of gestational diabetics did indeed show decreased adiposity when the mother was treated with insulin [92], babies born to insulin treated type 1 diabetics continued to show increased birth weight [93]. This lack of insulin effect on baby weight agrees with a former study, in which insulin showed good suppression of the free fatty acid levels [94]. The authors of that publication suggest that their findings do not support the fatty acid hypothesis and they favor the original Pedersen Hypothesis to explain fetal adiposity. A negative finding, however, does not point out why it is negative. It is possible, that while insulin suppressed free fatty acid levels, it had a lesser effect on maternal plasma triglycerides, which are probably the most significant fatty acid contributors to placental transport. Triglycerides are elevated in the plasma of type 1 diabetics [56,57]. Another possible explanation is that the almost unavoidable ups and downs of glycemic control in type 1 diabetics allows excessive glucose transfer at times, in-spite of injection-based insulin therapy. As the authors of the quoted paper [94] state, their findings do not support the fatty acid hypothesis, but one may also add: neither do those results refute it.

First appearance and accumulation of fat in the embryo received appropriate documentation, but still, important questions remained unanswered. In this paper, we suggest that excess fat tissue of the obese fetus probably shows increased cell numbers as well as larger than normal fat cells. Direct evidence proving this statement is yet to be collected. A work performed in rodents shows enhanced differentiation of white adipose cells in pups born to obese dams [95], such association was not shown in a small (n: 50) human study [96]. The finding of altered metabolic pattern [97] and greater potential for adipogenesis of mesenchymal cells (a potential precursor of adipocytes) obtained from infants born to obese mothers [98] appears compatible with the notion that these babies will develop hypercellular fat tissue. This question is more than of academic interest: it is well accepted that weight regain after weight loss is an extremely common occurrence [9,10], and that weight loss is mostly due to decrease of fat cell size and not to loss of fat cell number [17,18]. Accordingly, the number of fat cells in an individual remains relatively stable throughout his/her life, even after dieting and after weight loss.

The tendency to regain weight lost following life-style modifications (diet and exercise) is one of the significant issues contributing to the obesity epidemic. There is evidence that following weight loss, a major metabolic rearrangement takes place [13,99], resulting in decreased energy expenditure, increased hunger, increased food intake, and possibly even in more efficient extraction of calories from food ingested. Hormones and cytokines released from adipocytes [100–102] and neural impulses recorded from afferent fibers innervating adipose tissue suggest that fat cells probably signal their loss of volume or shrinkage of the cell membrane. Such signals reaching the hypothalamus or other neural centers may initiate the above suggested metabolic re-arrangements, which then will result in regain of weight, restoration of cell volume and stretching of the cell membrane. This restoration of status quo is probably most efficient in individuals who have been obese since childhood or since embryonic life, when distention of their adipocytes may have been epigenetically imprinted in their cell's memory as "normal." In contrast, among those gaining weight in adulthood, tissues may identify "status quo" as cell size or volume before their weight gain. In that context, loss of recently accumulated weight gained in adulthood may not trigger the robust humoral or neural responses that would result in quick regain in the weight.

Weight loss maintenance appears to be difficult under any circumstances but specially for "hypercellular" obese individuals, whose fat cell numbers remain stable even after weight loss. Therefore, the best

intervention would be obesity prevention rather than treatment. Prevention of hypercellular obesity would have to be attempted during pregnancy, when the adipocytes are recruited in greatest numbers. According to the hypothesis presented above, this can be approached by lowering fatty acid transport across the placenta in the second half of the pregnancy.

Lowering esterified and non-esterified plasma fatty acids of the pregnant woman without inflicting harm to her fetus is a formidable task. Some fatty acids are “essential” to the fetus. These are not synthesized by the fetus; instead, they have to be transferred from the mother. Others may have special roles and adequate quantity of these has to be available to the fetus. The dietary management is complicated by the need to avoid severely hypocaloric diets as these may induce harmful ketosis in the fetus. Because individuals may respond irregularly to low-fat/high-carbohydrate diets [103], a single diet may not be appropriate for all subjects. Special diets may have to be given to those with carbohydrate-induced hypertriglyceridemia [103]. Hypocaloric diet (even if combined with exercise) may not be sufficient to reduce the incidence of excessive fetal adiposity. A very recent study, which achieved its goal of preventing excessive maternal weight gain during pregnancy failed to prevent macrosomia or alter average birth weight (and presumably excessive fetal fat development] [104]. Finally, the use of any lipid-lowering pharmacological agent is severely restricted by the fear of causing harmful effects in the newborn. Though intervention may take place during intrauterine life, those who participate in such studies should continue to be monitored during their childhood, adolescence, and even adult life.

Large scale testing of the fatty acid hypothesis in humans will require the cooperative effort by endocrinologists, obstetricians, neonatologists, statisticians, nurses, administrators and other professionals – a complicated and expensive undertaking. Any attempt to test the hypothesis or to decrease fatty acid transfer across the human placenta has to be monitored for safety, effectiveness, internal validity, and procedural integrity. This has become possible by the recently available portable, patient operated devices that measure plasma triglycerides [105,106]. In concept these machines are similar to the widely used glucometers with which diabetic patients measure their own blood sugar levels several times daily. Those participating in such studies and those suspected to have obese or large for gestational age embryos in their womb should measure their own plasma triglyceride concentrations, with or without simultaneous glucose measurements. Monitoring free fatty acid levels, though not impossible, requires further technical advances to render such procedures fast, easy and inexpensive.

Testing the fatty acid hypothesis in animals (though less expensive and less time consuming than the above described large scale human study) presents other problems. Rodents commonly used in laboratories (mice, rats and guinea pigs) have bicornuate uterus, with large litters. The development of littermates at the lateral ends of the uterus is delayed over those nearer to the midline. In addition rodents have placental structure significantly different from humans. Furthermore, rat and mice pups are born with very small body fat content (not much more than 1%) only guinea pigs have body fat approaching 15%. These differences do not rule out meaningful animal studies, but make their results at least difficult to interpret and to validate them for their human equivalents. Further meaningful in vitro research could, however, be done on the cellular and molecular level to further elucidate the steps of adipocyte differentiation and its regulation.

The hypothesis presented above does not apply to all forms of obesity. It is, however, pertinent to a significant subsection, as the sum of gestational diabetic (include: pre-diabetic and Type 2 diabetic) and obese (include: overweight) represents a large segment of the pregnant population. Obesity of the pregnant woman, from whatever cause, increases the prevalence of obesity of her infant. Thus, a vicious circle [82] is created and serves to propagate obesity.

In summary, an expanded hypothesis is presented to explain the role of transported maternal plasma lipids not only as nutrients for fetal fat cell expansion, but perhaps also as initiators of fetal adipocyte differentiation. The hypothesis draws attention to the similarities of maternal plasma lipid elevations in two medical complications of pregnancy that are statistically associated with excess weight of the newborns. Finally, if the association of neonatal obesity and adult obesity holds true, the hypothesis opens a narrow window of opportunity during the second and third trimesters of pregnancy to slow down the progression of the obesity epidemic.

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