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REPRODUCTIVE EFFECTS OF MATERNAL METABOLIC DISORDERS: IMPLICATIONS FOR PEDIATRICS AND OBSTETRICS*

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The reproductive effects of metabolic disorders in women can be divided into four categories. The first of these is infertility. Galactosemia with its complication of ovarian failure is the disorder in this category. This complication may be prenatal in origin but whether this is so and its cause are unknown. The second category includes pregnancy effects of maternal metabolic disorders. The urea cycle disorder ornithine transcarbamylase (OTC) deficiency, maternal maple syrup urine disease and maternal homocystinuria are in this category. In the first two disorders, postpartum life-threatening illness due to metabolic crisis has occurred. Maternal homocystinuria is associated with a high risk for postpartum thromboembolic complications. The third category is the pregnancy effect of a fetal metabolic disorder. Pregnancies in which the fetus had long-chain hydroxyacyl-CoA dehydrogenase deficiency (LCHADD) have been complicated by the life-threatening (HELLP) syndrome during the third trimester. Rapid recovery of the mothers followed delivery, on occasion by emergency cesarean section. The fourth category is the fetal effects (teratogenicity) from a maternal metabolic disorder. The best-known example of this is maternal phenylketonuria (PKU), which produces microcephaly, mental retardation, congenital heart disease and intrauterine growth retardation. Treatment with a low phenylalanine diet begun before conception or no later than the earliest weeks of the first trimester markedly reduces the risk to the fetus and can result in normal offspring. Other examples of teratogenicity may include maternal homocystinuria and maternal hypothyroidism. *Key words: maternal metabolic disorder, fetus, reproduction, maternal PKU.*

In 1956 Professor Charles Dent commented that he knew of a mentally retarded woman with phenylketonuria (PKU) who had three retarded children, all without PKU. He thought that perhaps the PKU in the woman during pregnancy caused the retardation in the children[1]. We now know that this was the first published reference to maternal PKU and that Dent was correct in his assumption that maternal PKU is teratogenic[2,3].

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Maternal PKU is a major problem in PKU, perhaps the most important of several serious problems. Our recognition of its seriousness, however, has produced a focus on the teratogenic aspects of maternal metabolic disorders and endangered our overlooking other reproductive complications of metabolic disorders. Indeed, there are several areas in which reproduction or reproductive potential may be complicated by a metabolic disorder. These areas may be divided into four categories.

I. Infertility

The fact that women with PKU could become pregnant and bear children led us to believe that metabolic disorders do not affect fertility. Therefore, it was surprising to learn that females with galactosemia are infertile. In fact, despite even the earliest and most compliant treatment, galactosemia produces ovarian failure[4].

This complication of galactosemia was first reported by Kaufman et al.[5], although there was previous indication of streak ovaries in galactosemic women[6]. The first hint of an ovarian problem in these girls is hypergonadotrophism. Within even the first few months of age, the serum concentration of follicle stimulating hormone (FSH) is very high (Table I). At pubescence, these girls usually either do not menstruate or will experience only an initial menstrual period followed by amenorrhea. Occasionally, girls will menstruate but will be oligomenorrheic. In addition, secondary sexual changes do not appear. On the basis of pelvic ultrasonography, the ovaries are usually very small or cannot be visualized[8]. When directly examined, the ovaries are usually only streaks of stroma completely or almost completely devoid of follicles and oocytes[7]. An international survey of galactosemia reported the complication of ovarian failure in over 70 percent of girls with galactosemia[8].

Table I: Serum Follicle Stimulating Hormone (FSH) Levels in Females with Galactosemia

Age (yrs)	FSH (mIU/ml)*
1/12	29
7/12	40
8/12	13
2	54
13	65

* Normal FSH value is < 4 mIU/ml

The origin of the ovarian failure in galactosemia is unknown. We have reported morphologically normal ovaries in a neonate with galactosemia[9] and have found this to be so in a second galactosemic neonate. This suggests that the damage could be postnatal. On the other hand, Chen et al.[10] have found that rats exposed to galactose prenatally have markedly reduced numbers of oocytes. Moreover, as seen in Table I, serum FSH is markedly increased in galactosemic females as early as the first few weeks of life, virtually identical to Turner syndrome. Moreover, even with the strictest dietary treatment, the complication occurs. These observations suggest that a prenatal factor is either solely responsible for the ovarian failure or is a major cause of the problem. One theory as to its cause was that of reduced uridine diphosphate galactose (UDPGal)[11], a product of the galactose-1-phosphate uridyltransferase reaction that is blocked in galactosemia (Fig. 1). Presumably, reduced UDPGal would be present in the fetus as well as in the infant after birth. As shown in Table II, the Los Angeles group has found that classic galactosemics with ovarian failure have reduced UDPGal, while females with variant galactosemia who have some residual transferase activity have normal UDPGal levels and normal ovarian function[4]. However, supplementation of these girls with uridine, which raises the UDPGal levels to normal, does not prevent ovarian failure[12].

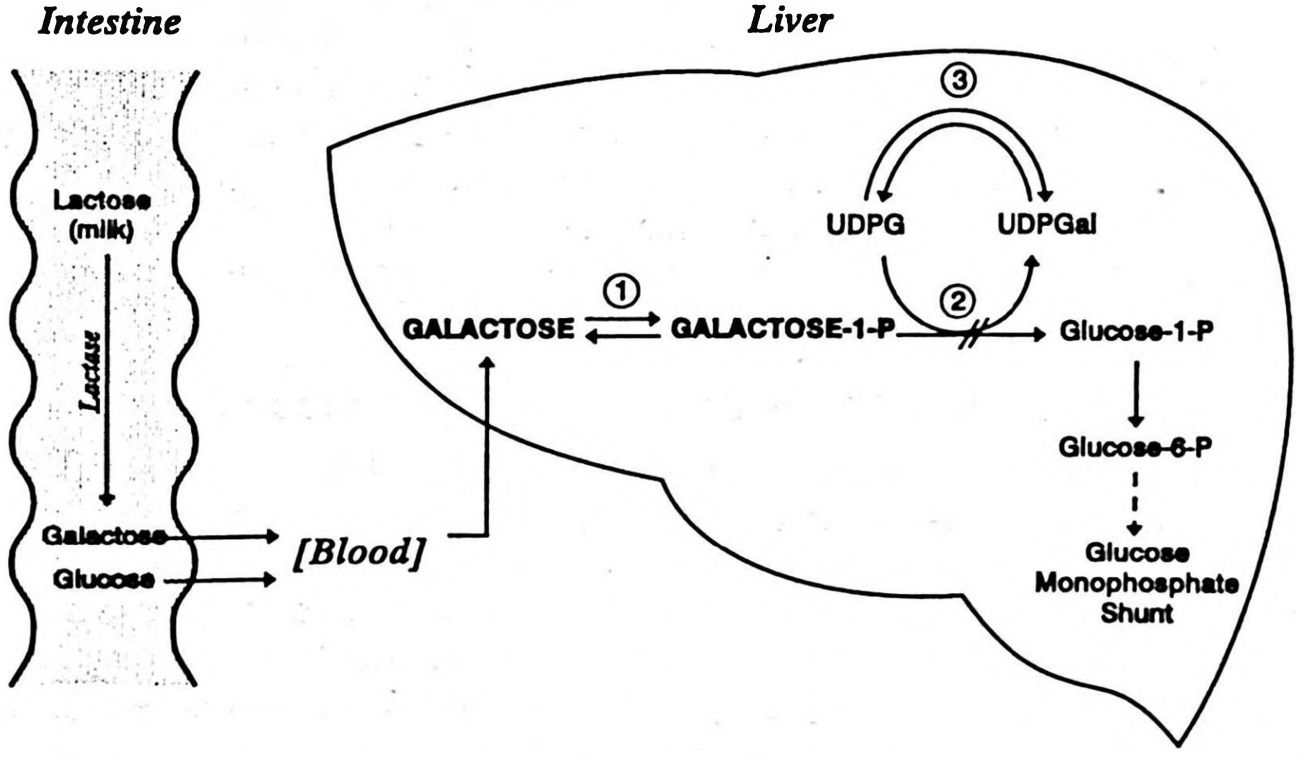

Fig. 1: Galactose metabolism from its liberation from lactose in the intestine through its metabolism. The enzymes required for galactose metabolism are (1) galactokinase; (2) galactose-1-phosphate uridyltransferase (GALT); (3) uridine diphosphate-4-epimerase. In galactosemia, the defective enzyme is GALT, resulting in accumulations of galactose-1-phosphate and galactose and reduced UDPGAL.

Table II: RBC Uridine Diphosphate Galactose (UDPGal) and Ovarian Function in Classic and Variant galactosemia

Classification	RBC UDPGal (umol/100 gm Hgb)	FSH	Ovarian function
Classic galactosemia	3.9	38	Failure
Variant galactosemia	9.4	6	Normal
Normal individuals	10.3	<9	Normal

So far, galactosemia is the only inborn error known to have direct effect on gonadal function. Even in galactosemia, this effect seems to target ovaries and to spare the male gonad[5,13]. Nevertheless, as children with other early treated inborn errors survive to adolescence and adulthood, it will be important to study them carefully for sexual maturation and fertility.

What are the implications for treatment in galactosemia? First, parents of newly diagnosed female infants must be fully informed about the probability that they will develop this problem despite early treatment. Second, gonadotrophins, particularly FSH, should be measured within the first year of life so that ovarian unresponsiveness can be detected. Finally, girls with ovarian failure should be evaluated by pediatric endocrinologists at or before pubescence and, if secondary sexual characteristics are not appearing, given normal therapy to stimulate their appearance. Otherwise, these girls will suffer not only from infertility but also the psychosocial problems that occur from lacking the appearance of sexual maturation.

PREGNANCY EFFECTS OF MATERNAL METABOLIC DISORDERS

Maternal PKU once again lulled us into complacency, this time regarding the safety of pregnancy itself when the woman has a metabolic disorder. After all, women with PKU have withstood pregnancy well. That has also been true of women with histidinemia and several other maternal inborn errors that have come to our attention. Recently, however, we have learned that for women with still other maternal disorders, pregnancy can be a threat. The threat seems to be greatest during the postpartum period. For instance, three women heterozygous for X-linked ornithine transcarbamylase (OTC) deficiency are known to have developed hyperammonemia with coma or other severe symptoms three to eight days following delivery. Two of these women died[14]. A woman with maple syrup urine disease became dizzy and lethargic nine days postpartum with a very

increased blood leucine level; she recovered after her carbohydrate intake was increased[15]. At least three women with homocystinuria have had major thrombotic episodes postpartum[16-18]; one of the women died. The postpartum complications in OTC deficiency and maple syrup urine disease were clearly linked to exacerbation of the biochemical abnormalities. This was not studied in the women with homocystinuria, but could also be true for that disorder. We have noted huge postpartum increases in plasma histidine and phenylalanine in maternal histidinemia and maternal PKU, respectively. These biochemical exacerbations are probably secondary to postpartum catabolism and proteolysis and represent a major threat in childbearing to women with certain metabolic disorders.

PREGNANCY EFFECT OF A FETAL METABOLIC DISORDER

Wilcken and her colleagues have reported severe liver disease and other features of the HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome during the third trimester of pregnancy in otherwise healthy women carrying fetuses with the fatty acid disorder known as long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency[19]. The women rapidly recovered following delivery, in some cases by emergency cesarean section. It seems likely that one or more of the biochemical abnormalities, perhaps the hydroxydicarboxylic acids, in these affected fetuses crossed the placenta and were toxic to the maternal liver. So here, the fetus damages the mother, a fascinating converse to the final and most frequent of the reproducive problems in which the mother with a metabolic disorder damages the fetus. The fetus-damages-the-mother problem could occur more frequently in women carrying fetuses affected with disorders than we realize. This might be especially so for those fetuses with inborn errors of organic and fatty acids.

FETAL (TERATOGENIC) EFFECTS OF MATERNAL METABOLIC DISORDERS

The major reproductive problem among the metabolic disorders is that of fetal effects from a maternal metabolic disorder. The most frequent and dramatic of these is maternal PKU.

Maternal PKU is a fetopathy syndrome that produces microcephaly, mental retardation, congenital heart disease and intrauterine growth retardation. In fact, this can be a devastating condition with frequencies of birth defects perhaps the highest known in medicine from a single cause. For instance, when the mother has classic PKU, the frequency of mental retardation in the offspring may be as high as an astounding 92 percent, and that of frank microcephaly as high as 73 percent[3]. This has become a major problem in PKU, perhaps the major current problem in PKU. If mental retardation from maternal PKU cannot be prevented, we are in danger of replacing in the next generation the number of retarded individuals who are being removed from the current generation by

newborn screening and early treatment of PKU[20]. Ironically, this is a potential problem born of success – the success that has virtually eliminated mental retardation in girls with PKU and now allows them to be in the social position of reproducing.

Can this potential tragedy be prevented? We do not yet know. However, there is hope. Evidence from case reports and, most recently, from the Maternal PKU Collaborative Study as shown in Table III, indicates that low phenylalanine dietary treatment when begun prior to conception or within the first 10 weeks following conception might prevent the fetal damage[21]. This table, however, does not answer the question of whether even the best treatment of maternal PKU results in children who are completely normal. Only long-term follow-up of these and other study children will answer this important question.

Table III: Outcome of Offspring from Treated Maternal PKU Pregnancies in the Maternal PKU Collaborative Study

Onset of treatment (gest. wks)	Birth measurement (median centile)			IQ (mean)
	Weight	Length	Head Circumference	
Before conception	70	78	49	107*
0-10	56	78	43	107*
10-20	49	56	31	87
> 20	21	26	10	69

* IQ score refers to treatment onset before conception and to 10 wks gestation.

If favourable results in the treatment of maternal PKU are to be achieved, an understanding of pathogenesis is critical. Perhaps this can be illustrated by another facet of the maternal PKU fetopathy, the dysmorphic facies first reported by Bovier-Lapierre and colleagues[22]. The features of this facies include midface hypoplasia, short palpebral fissures, epicanthal fold, anteverted nares, and elongated philtrum. Interestingly, this facies and that in the fetal alcohol syndrome are virtually identical. In fact, there is a striking similarity between maternal PKU and fetal alcohol syndrome, as listed in Table IV. This similarity suggests that these two syndromes share a common pathogenesis. Perhaps phenylalanine and alcohol, both micromolecules that readily cross the placenta, act at the same control points of development. If so, to understand one syndrome could allow us to understand the other.

Tablo IV: Fetopathies of the Maternal PKU and Fetal Alcohol Syndromes

Fetopathy	Maternal PKU	Fetal Alcohol
Microcephaly	Yes	Yes
Mental retardation	Yes	Yes
Hyperactive behavior	Yes	Yes
Congenital heart disease	Yes	Yes
Dysmorphic facies	Yes	Yes
Intrauterine growth retardation	Yes	Yes

The focus has usually been exclusively on maternal PKU. But what about non-PKU mild hyperphenylalaninemia? There are almost as many girls and young women with mild hyperphenylalaninemia (MHP) known to clinics and newborn screening programs as those with PKU. For years it has been clear that maternal MHP with blood phenylalanine levels between 180 and 720 umol/L (3-12 mg/dl) is less damaging to the fetus than maternal PKU with its higher phenylalanine levels and, in some cases, seemed not to cause damage at all[23]. The question is whether MHP in the pregnant woman is at all teratogenic. From an international survey of untreated maternal mild hyperphenylalaninemic pregnancies, we have found that when the maternal blood phenylalanine level in MHP is less than 400 µmol/L (6.5 mg/dl), birth measurements are not appreciably altered from normal expectation and the median offspring IQ is 108, whereas when the maternal phenylalanine level exceeds 400 µmol/L, birth weight and birth head circumference are significantly lower and the median offspring IQ drops to 100[24]. The relevant data are shown in Table V.

Are these reductions sufficient to justify identifying and treating women with MHP through their pregnancies, many of whom have never been on the diet or perhaps were never even informed that they have a phenylalanine "problem"? This is a

Table V: Offspring Outcome in Survey of Untreated Maternal Mild Hyperphenylalaninemia

Maternal blood phenylalanine (µmol/L)	Birth measurement (Median Z-Score)			IQ (median)
	Weight	Length	Head Circumference	
< 400	.08	.38	-.30	108
> 400	-.36	.16	-.76	100

major current and future question. Our current policy is to recommend dietary treatment when the blood phenylalanine level is consistently greater than 400 µmol/L (6.5 mg/dl).

What are the implications of maternal PKU and maternal non-PKU MHP for newborn screening programs? Is follow-up from newborn screening identification sufficient to guarantee that these young women will be known and will be given the proper advice when they reach childbearing age? What about women with PKU born before newborn screening or in countries without universal newborn screening? Is routine premarital and/or prenatal screening for PKU required? If routine screening at these times is necessary, is it logistically possible? Is newborn screening in most programs sufficiently sensitive to identify infants with non-PKU MHP as well as those with PKU? Or do we miss many or most of the infants with MHP? Is this important in the consideration of maternal MHP? These and many other questions face us. The answers to these questions depend on the answers to the many questions about maternal PKU and maternal MHP that we still have not answered.

Finally, is PKU the only inborn error with maternal implications for the fetus, or are there other inborn errors in the same category? So far, no other maternal inborn error has been found to have the implications of maternal PKU. In fact, a surprisingly large number of maternal inborn errors seem to be benign to the fetus. These include histidinemia[25], hyperprolinemia[26], the HHH syndrome (hyperornithinemia-hyperammonemia-homocitrullinuria)[27], tryptophanemia[28], maple syrup urine disease[15], organic acid disorders such as isovaleric acidemia[29] and propionic acidemia[15], the urea cycle disorder, argininosuccinic acidemia[30], cystinosis[31], Hartnup disorder[32], galactosemia, in the few pregnancies that have occurred[33], and even tyrosinemia[34], which is strange since tyrosine is chemically so similar to phenylalanine. It is possible that maternal homocystinuria, particularly the B_6-unresponsive form, produces mental retardation and congenital anomalies in the offspring, but this is based on only a couple of cases[35]. Notably, maternal hypothyroidism could have major implications for the cognitive development of the offspring[36]. If so, girls with congenital hypothyroidism prevented from becoming mentally retarded by newborn screening and early treatment could in future years form a cohort in danger of having damaged children that might even be considerably larger than the cohort of maternal PKU.

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