

whose diagnoses were made later on clinical grounds had negative results on newborn screening.

Although results showed an increase in the rate of diagnosis following the introduction mass spectrometry screening in newborns, most of the increase could be accounted for by the diagnosis of medium-chain acyl-CoA dehydrogenase deficiency and to a lesser extent by the diagnosis of other disorders of fatty acid oxidation.

The authors calculated the cost of establishing a diagnosis. The incremental cost of the tandem mass spectrometry screening was \$0.70 (USD) per newborn. The cost of confirmatory testing was \$217 and the cost per relevant disorder detected was \$3,939 if PKU was excluded or \$2,519 if it was included. They concluded that their approach provides a rapid and inexpensive way to screen for a wide range of very rare metabolic diseases and that it identifies more cases than are diagnosed clinically. However they caution that it is not yet clear which patients identified through newborn screening would have become symptomatic if screening had not been performed.

Wilcken B et al. *New Eng J Med* 2003;348:2304-2312.

**Editor's Comment:** *This paper brings to the fore the debate over the extent to which tandem mass spectrometry technology should be used to screen for a growing number of inborn errors of metabolism. As*

*noted in a recent article by Marshall,<sup>1</sup> the debate pits parents and often physicians who advocate the application of this technology against ethicists with concerns over costs and public health officials with concerns over how the potentially large amount of genetic data will be managed. The Wilcken study demonstrates the successful implementation of the technology in a public health setting. It documents that the technology leads to an increased rate of diagnosis at low cost, especially for disorders of fatty acid oxidation, although acknowledges the possibility that some patients diagnosed as newborns may not have become symptomatic if screening had not been performed. Readers should note that metabolic screening by tandem mass spectrometry was highlighted by a recent lead article in GGH.<sup>2</sup> This article explains how technology works, provides guidelines for its use and describes its successful application in North Carolina. Together, these articles provide support for advocates of wider use of tandem mass spectrometry for newborn screening.*

## References

1. Marshall E. *Science* 2001;294:2272-2274.
2. Millington D, Koeberl D. *GGH* 2003;19:32-38.

William A. Horton, MD

## The Effect of Clitoral Surgery on Sexual Outcome in Individuals Who Have Intersex Conditions with Ambiguous Genitalia: A Cross-Sectional Study

It is estimated that intersex conditions occur in one per 2,000 live births. In the past, treatment had been based on the assumption that infants were gender neutral at birth, and that assignment of sex of rearing in early years which is reasonably compatible with the appearance of the external genitalia would provide a normal gender identity and partner orientation in adulthood. Subsequently, it has been recognized that there is a complex interaction between prenatal and postnatal factors that lead to the development of gender and sexual identity.

In the United States and in most western European societies, female rearing was most frequently recommended to parents whose infant had ambiguous genitalia. When the decision to raise the child as a female was made, surgery was usually undertaken to remove any ambiguity of the genitalia and to feminize the external appearance. This was done with the hope of a good psychosocial outcome.

Minto et al undertook a study involving individuals with several intersex conditions which included ambiguous genitalia, and who were living as adult females. Individuals were recruited from the Androgen

Insensitivity Syndrome Support Group, the Adrenal Hyperplasia Network and the Intersex Clinic at University College in London Hospital.

Questionnaires were distributed and individuals could respond anonymously or identify themselves, in which case, their records would be examined with their permission. The self-administered questionnaires included the Golombok-Rust inventory of sexual satisfaction (GRISS) for women. Of the 39 patients included in this study, 11 had no clitoral surgery and 28 had had clitoral surgery. Almost all individuals who had undergone gonadectomy were taking hormone replacement therapy. Historical trends were noted in that most individuals seen before 1979 had undergone clitorrectomy, while those operated on since 1980 usually underwent nerve-sparing clitoral reduction surgery. Many individuals also had vaginal reconstructive surgery.

The authors did multiple types of analysis of the data; however, the bottom line is that of the 39 participants, 13 individuals had never been sexually active and the 28 sexually active individuals had below normal scores in terms of sexual function. A low score on sensuality

was evident in the clitoral surgery group when compared to the non-surgical group. Both groups had difficulty with orgasm, which is relatively rare in a sexually healthy population. Of the 28 who had clitoral surgery, 18 found it impossible to have orgasm, compared with none among those who had not had clitoral surgery.

It was difficult to determine exactly why most of the study individuals were having difficulty with sexual function because only a questionnaire was used to obtain the data. There did not appear to be a difference among those patients recruited from the clinic versus those in support groups.

It would appear that genital surgery at a young age did not lead to satisfactory gender identity and sexual activity. However, it is not clear what the most appropriate approach should be. The authors encourage debate about the ethical issues, the development of reliable information, support of research in this area and how important it is to share this information with parents and patients who are considering clitoral surgery.

Minto CL et al. *Lancet* 2003;361:1252-1257.

**First Editor's Comment:** *The outcomes of the management of intersex are not perfect. This study following up on previously treated individuals suggests that clitorotomy does not lead to sexual satisfaction, however, neither does clitoral reduction. Clearly, more research and discussion are needed in this area.*

Judith G. Hall, OC, MD

**Second Editor's Comment:** *As the authors acknowledge, interpretation of their study is hampered by the small number of study subjects and the possibility that those electing to participate were among the more*

*dissatisfied patients contacted initially. Quite interesting are the data that indicate that clitoromegaly itself is associated with sexual dysfunction. In addition to the concept that clitoral recession will permit the child to more readily accept her female sex assignment, the procedure is performed to ease parental acceptance of their newborn child. Those who have dealt on a personal and daily basis with parents of children with ambiguous genitalia know the need to assure and reassure parents is a paramount goal which is difficult to attain. Early clitoral recession by a skilled surgeon is most often recommended by this writer in those neonates with more severe degrees of genital ambiguity.*

*Because of widespread neonatal screening for CAH, there is an increasing number of females with the most severe form of genital ambiguity known as Prader V or complete incorporation of the urethra into the phallus/clitoris. In the opinion of this writer and many others it is inappropriate to rear these genotypic and potentially fertile girls as males, thus necessitating genital surgery. Since both clitoromegaly and clitoral surgery impede sexual satisfaction, the challenge is to devise a corrective procedure that does not do so.*

*It would have been of interest to learn whether in those women with ambiguous genitalia who did not undergo clitoral surgery, clitoromegaly during childhood and young adulthood was a matter of significant concern. Counseling girls with ambiguous genitalia, whether operated upon or not, needs to begin in mid-childhood and to be conducted by individuals skilled in the management of this problem, as mentioned by Slijper in an excellent commentary regarding this article, in the same issue of *Lancet* (2003;361:1236-1237).*

*Minto's article also provides further support for the antenatal treatment with glucocorticoids of women bearing female CAH offspring at risk for development*

Table

**Sexual function of 28 participants, according to GRISS**

	Subscale scores (%)			Subscale scores (%)		
	Clitoral surgery group (n=18)			No clitoral surgery group (n=10)		
	Normal*	Difficulties†	Severe difficulties‡	Normal*	Difficulties†	Severe difficulties‡
Frequency	28%	72%	33%	30%	70%	30%
Communication	28%	72%	17%	20%	80%	20%
Satisfaction	61%	39%	0%	80%	20%	0%
Avoidance	28%	72%	22%	20%	80%	10%
Sensuality	22%	78%	22%	80%	20%	10%
Vaginal penetration§	33%	67%	33%	33%	67%	22%
Orgasm	39%	61%	28%	60%	40%	0%

\*Score of 1-4. †Score 5-9. ‡Score of 8 or 9. §Four individuals chose not to answer the question on vaginal penetration.

Adapted from Minto CL et al. *Lancet* 2003;361:1252-1257.

of ambiguous genitalia. It will be of great interest to assess the psychosexual development, orientation, and sexuality of these subjects as adult women. With the observations collected to date the impression is that they are normal little girls.

Allen W. Root, MD

**Third Editor's Comment:** The topic of intersex management, outcome, and research has received much attention in the past 2-3 years. The reader should be aware of publication of a collection of excellent papers

presented in May 2002 at a conference entitled "Genetic and Hormonal Basis of Sexual Differentiation Disorders" (*The Endocrinologist* 2003;13:175-287) and of a "Summary of a Research Workshop on Intersex" held in sequence with the above conference (to be published in *The Endocrinologist*). Furthermore an excellent review entitled "Management of Children with Intersex Conditions: Psychological and Methodological Perspectives" by S. Berenbaum was presented in *GGH* 19:1.

Robert M. Blizzard, MD

## Neonatal Exendin-4 Prevents the Development of Diabetes in the Intrauterine Growth Retarded Rat

Intrauterine growth retardation (IUGR) has been shown to be associated with significant adult morbidity, including insulin resistance, reduced pancreatic  $\beta$ -cell mass, and subsequent type 2 diabetes. Uteroplacental insufficiency, a cause of IUGR, limits the availability of substrates, growth factors, and hormones to the fetus. A rat model of IUGR can be induced with bilateral uterine artery ligation at 19 days of the 22 day gestation period. In rats during the newborn period there is extensive remodeling of the pancreas brought about by  $\beta$ -cell replication, neogenesis and apoptosis. A second wave of neogenesis occurs during weaning.

The incretin hormone glucagon-like polypeptide-1 (GLP-1) stimulates pancreatic neogenesis and increases  $\beta$ -cell mass. Therefore its administration to rat pups who have undergone 90% partial pancreatectomy results in an increase in both  $\beta$ -cell mass and improved glucose homeostasis. Exendin-4 is a long-acting GLP-1 which in addition to the aforementioned activities stimulates expression of Pancreatic Duodenal Homeobox (PDX) protein in the pancreas. PDX is critical for the early development of both the endocrine and exocrine pancreas and mediates glucose responsive stimulation of transcription of the insulin gene.

Stoffers and colleagues treated IUGR rat pups with exendin-4 during the early postnatal period to study its effects on the subsequent development of type 2 diabetes. Four groups of rat pups were studied: (1) control pups given vehicle injection, (2) control pups given exendin-4 injections, (3) IUGR pups given vehicle injections, and (4) IUGR pups given exendin-4 injections. Injections were administered on postnatal days 1 through 6. Glucose tolerance,  $\beta$ -cell mass,  $\beta$ -cell proliferation and PDX gene expression were measured at 14 days and 3 months of age. Glucose tolerance was also determined at 7 weeks and 8 months of age.

Exendin-4 decreased weights in both control and IUGR pups (Groups 2 and 4) at 2 weeks. This decrease persisted into adulthood (Table). At day 14, glucose

tolerance in the IUGR pups treated with exendin-4 was similar to that in control animals. The treated animals remained euglycemic at 8 months. Vehicle-treated IUGR pups (Group 3) developed diabetes by 3 months and died by 8 months of age. Exendin-4 treated IUGR pups (Group 4) had normal  $\beta$ -cell mass comparable to that in Group 1 as the result of normalized replication rates. While Pdx-1 mRNA levels were reduced by 60% in IUGR rats not receiving exendin-4 at 14 days, those treated with exendin-4 had normal levels.

The authors state their major finding is that a short treatment with exendin-4 during the early newborn period prevents the development of diabetes in the IUGR rat. It is not clear whether this effect is through the stimulation of Pdx-1. However, the effect is independent of  $\beta$ -cell mass, since its effects were observed prior to any reduction in the IUGR pancreatic mass. They suggest that the permanent improvement in maintenance of  $\beta$ -cell mass by exendin-4 may mean that similar drugs could be effective in reducing the risk or preventing type 2 diabetes mellitus in individuals born with IUGR. The negative part of the study was the growth inhibiting effect of exendin-4.

Stoffers DA, et al. *Diabetes* 2003;52:734-740.

Treatment group	2 weeks (g) (n=9)	3 months (g) (n=7)
Control vehicle	27.7 $\pm$ 0.3	331.7 $\pm$ 7.0
Control Ex-4	22.2 $\pm$ 0.6*	305.3 $\pm$ 12.7*
IUGR Ex-4	13.8 $\pm$ 0.7†	311.0 $\pm$ 4.0†
IUGR vehicle	17.2 $\pm$ 0.7‡	351.7 $\pm$ 26.2‡

Data are means  $\pm$  SE. \*P < 0.05 control Ex-4 vs. control vehicle; †P < 0.05 IUGR Ex-4 vs. IUGR vehicle; ‡P < 0.05 control vehicle vs. IUGR vehicle.

Adapted from Stoffers DA, et al. *Diabetes* 2003;52:734-740.