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Additional indications for genetic counseling in women of advanced maternal age

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The University of Arizona, 1988

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ADDITIONAL INDICATIONS FOR GENETIC COUNSELING IN WOMEN OF ADVANCED MATERNAL AGE

by

Francis Myron Hays

A Thesis Submitted to the Faculty of the

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STATEMENT BY AUTHOR

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ABSTRACT

Genetic counseling for women with advanced maternal age is well established medical standard of care. However, only one study has yet been done to test the validity of that policy. Records of 283 patients referred for genetic counseling with advanced maternal age as a primary indication were examined. Of these, 57.6% had at least one additional indication. This value did differ significantly from Rubin's data which reported a 43.3% rate (X^2=13.01, p>0.001). The additional indications were broken down according to McKusick's system, and a statistical difference between my and Rubin's data was found in the autosomal dominant, autosomal recessive, potential teratogenic exposure and miscellaneous categories. There was no significant statistical difference between my and Rubin's data in the X-linked, chromosomal anomalies and multifactorial groups. These data underscore the need for physicians to refer patients with advanced maternal age for genetic counseling, and provides a scientific basis for doing so.

INTRODUCTION

Since 1975 genetic counseling has been an officially recognized field of medical expertise. However, the concept of genetic counseling has been around for far longer. Few would argue that Galton was one of the first genetic counselors, and eugenics made the first systematic attempt to provide people with information about their risks for certain diseases. However, the motives of these early attempts at genetic counseling raised serious moral and ethical questions. Thus, after World War II and the German excesses based on an ideal of a "master race," the idea of providing reproductive information to women based on their genetic constitutions was largely ignored. It was not until 1968 when Sarah Lawrence College initiated a formal genetic counselor training program that the field received serious consideration.

Since that time, it has been necessary to define what genetic counseling could and could not do. The standard definition for genetic counseling is that drafted by the American Society for Human Genetics. It reads as follows:

> Genetic counseling is a communication process which deals with the human problems associated with the occurrence, or risk of occurrence, of a genetic disorder in a family. This process involves an attempt by one or more appropriately trained persons to help the individual or family

> to (1) comprehend the medical facts, including the diagnosis, probable course of the disorder, and the available management; (2) appreciate the way in which heredity contributes to the disorder, and the risk of recurrence in specified relatives; (3) understand the alternatives for dealing with the risk of recurrence; (4) choose the course of action which seems to them appropriate in view of their risk, their family goals, and their ethical and religious standards, and to act in accordance with that decision; and (5) to make the best possible adjustment to the disorder in an affected family member and/or to the risk of recurrence of that disorder.[1,2]

This definition points out the two broad goals of genetic counseling: education[3-15] and prevention[16-23]. Assuming this to be true one would expect to find fairly good agreement in the literature regarding indications for genetic counseling. One does. Widely accepted indications for genetic counseling include: exposure to a potentially teratogenic agent, a previous birth of a child with a birth defect, a family history of children with birth defects, a family history of genetic disease or a risk for a disease because of family ancestry, multiple spontaneous abortions and advanced maternal age[24-33]. Except for the first and last indications, the need for genetic counseling is fairly obvious and there exists little doubt that people would benefit from it. Teratogen counseling raises many issues with which this thesis will not deal. Referral for counseling because of advanced

maternal age is the subject of this thesis.

With the exception of chromosomal anomalies, there is no empirical proof that older women are at any higher risk for any specific reproductive problem related to genetics[34-40]. Given that fact, it would seem reasonable to ask if there are sufficient other reasons for counseling. If there are not sufficient indications for counseling, then two ethical issues arise: the use of a limited resource[41,42] and possible stress on a woman already at a difficult time in her life[43-48].

To date, only one study has attempted a systematic look at women with advanced maternal age to assess what other indications for counseling might exist, other than an increased risk for offspring with chromosomal anomalies. Rubin's study[49] was undertaken to validate the need for genetic counseling prior to amniocentesis for women over 34 years of age at the time of parturition. Even though the data were clinically significant, reproducibility has not been sought. This study will attempt to see if there exists, in reality, an empirically high rate of indications for genetic counseling in women 35 years of age and older and to check for the reproducibility of the original data set forth by Rubin.

MATERIALS AND METHODS

The files of 283 women with a primary indication for genetic counseling of advanced maternal were reviewed. All were evaluated by a genetic counselor associated with University Medical Center in Tucson, Arizona and accredited by the National Society for Genetic Counseling. Each pedigree was examined and any indication or indications for genetic counseling were tabulated. In addition, the familial cancers were scored and included except when sex specific cancers occurred outside of the specified sex's line of descent. All data were then classified after McKusick[50] (Tables I-VIII). In addition, defects attributed to multifactorial inheritance, chromosomal anomalies, cancers and teratogenic agent exposure data were tabulated. A few indications that were not easily classified were categorized as "miscellaneous." Effort was extended to make sure that the data were classified in a manner that would be consistent with the pedigree. In addition, if the indication occurred more than one time, it was only listed once. For example, if both parents were at risk for Tay Sach's disease due to French Canadian ancestry,

there would be only one listing for Tay Sach's recorded in the data for that family. Data were then compared to Rubin's data using the Chi square test with one degree of freedom.

RESULTS AND DISCUSSION

Of the 283 families, 163 (57.6%) had at least one other indication for genetic counseling beyond advanced maternal age. Twenty-nine (10.2%) of the families had a relative with cancer but no reported additional indications. The remaining 91 (32.2%) of the families had no additional reported indications.

The first figure, 57.6%, differs significantly from Rubin's data which reported a 43.3% indication rate for genetic counseling (X^2= 13.01, p>0.001). This difference in rates may have several possible explanations: Rubin's use of several counselors and, by extension, several counseling and recording styles; the use of a higher socio-economic class composition of patients in my study suggesting a greater general knowledge base, and, therefore, a better knowledge of family history; or a simple variation in sampling style. Of these three, the second explanation seems most likely and raises the fewest additional questions. Nevertheless, it would seem prudent to undertake a much more extensive study in the future to determine which of the two studies is closer to the mean, or if they represent two extremes on a continuum.

Tables I through VIII show indications for genetic counseling classified according to the type of disorder. Twenty-six (9.5%) of the 192 families with an indication had an autosomal dominant disorder (Table I). Sixty-five (23.0%) indications were for an autosomal recessive trait (Table II). Two (0.71%) and 18 (6.4%) of the diseases fit a pattern due to X-linked (Table III) and chromosomal anomalies (Table IV), respectively. Fifty-seven (20.1%) of these families had a disease with a multifactorial mode of inheritance (Table V). Familial cancers (Table VIII) and potential teratogenic exposures (Table VI) were found in 69 (24.4%) and 6 (2.1%) of the family units, respectively. The remaining 64 (22.6%) indications for genetic counseling were termed "miscellaneous" (Table VII). Since some of the families had more than one indication, the percentages exceed 100%.

Of the individual categories of disorders, only the chromosomal (X^2= 0.6, p=0.50-0.75), multifactorial (X^2=0.07, p=0.10-0.25) and X-linked (X^2= 1.0, p=0.10-0.05) traits did not differ significantly from my data and Rubin's data. The similarities between my data and Rubin's data are best explained by the unusual nature of these disorders, thus making it more likely that they

would be remembered by the family. With respect to chromosomal anomalies, the fact that they have been well described and are easily diagnosable make misdiagnosis unlikely.

The autosomal dominant (X^2= 11.7, p>0.005), autosomal recessive (X^2= 4.16, p= 0.05-0.001), miscellaneous (X^2= 129.9, p> 0.005) and potential teratogenic exposure (X^2= 8.0, p>0.005) indications were all significantly different from Rubin's data. This may be explained by the fact that some autosomal dominant and autosomal recessive conditions are easily missed or misdiagnosed by a clinician and tend to have such unusual names that families may not remember the diagnoses. Potential teratogenic exposure is often area specific (such as Trichloroethylene in Southern Arizona) and may not always be reported by the family, occasionally for fear of legal reprisal. Finally, the differences may also arise from the differing geographical areas as Rubin's data came from New York City and mine from Southern Arizona with all the associated cultural, economic and social differences.

Rubin's data did not include familial cancers although this group was considered in the present study. Because markers for genes associated with various cancers

are already available (e.g., colo-rectal cancer) and many more markers are being sought, knowing a family's history of cancer might be beneficial in counseling about risks for specific tumor development in family members. It might also enable the family to make informed life style decisions which could lower risks for tumor development based on the information. Although it is unlikely that any reproductive decisions would be made based on cancer risks, providing a risk estimate is well within the genetic counselor's role as educator.

CONCLUSION

This study has attempted to investigate the additional indications for genetic counseling in women receiving counseling because of advanced maternal age. Of the 283 files examined, 57.6% had at least one other indication. Ten and two tenths of a percent of the families reported a relative with cancer, but no other indications. Reporting no additional indications for counseling were 32.2% of the families. The autosomal dominant, autosomal recessive, potential teratogenic exposure and miscellaneous indications differed significantly from the published data. Although my data differ significantly from those published, valid reasons for accepting my results include my use of a higher socio-economic class, a better educated population and simple geographical differences.

These data underscore the need for genetic counseling in women with advanced maternal age (at least 35 years of age). This report, along with that of Rubin, shows that advanced maternal age is not the sole indication for genetic counseling in these women. These findings should indicate to primary care physicians that genetic

counseling should be incorporated into routine prenatal care.

As I have shown, the rate of additional indications for genetic counseling in women of advanced maternal age is exceptionally high. In an era of cost control measures being placed on medicine these data show how crucial it is for women to receive a complete genetic evaluation in order to provide reproductive information about previously unexpected risks. The fact that over one half of the women in my sample had additional counseling issues ascertained at the time of the genetic counseling session should put to rest any questions about the ethics of counseling the relativly small group of pregnant women of advanced maternal age. This study also points out the need for counselors of pregnant women of advanced maternal age to be trained in the principles of genetics and reproductive medicine. As more women delay conception until they are older, the need for thoroughly trained genetic counselors will grow[51] and further research in this area will be needed. Data from this study imply that genetic counseling for advanced maternal age is valid, and empirical data make it unethical not to provide the option of such services to this population.

Table I

Indications for Genetic Counseling from Pedigree Data:

Autosomal Dominant Traits

Adult Polycystic Kidney Disease	1
*Arthritis	1
*Best's Disease	1
*Dyslexia	2
Friedreich's Ataxia	1
Huntington's Disease	2
Manic Depression	8
*Narcolepsy	4
Osteogenesis Imperfecta	2
*Patent Ductus Arteriosus	1
Polydactyly	1
*Syndactyly	1
Tuberous Sclerosis	1

* Disorder has genetic heterogeneity, but appears to follow an autosomal dominant pattern.

Table II

Indications for Genetic Counseling from Pedigree Data:

Autosomal Recessive Traits

*Bilateral Microtia	1
*Congenital Deafness	3
Cystic Fibrosis	3
*Dwarfism	3
*Gastroschisis	1
*Hodgkin's Disease	1
*Hydrocephalus	3
Kuf's Disease	1
Pendular Nystagmus	1
Retinitis Pigmentosa	1
*Situs Inversus	2
Tay Sach's Carrier Possibility	43
Thalassemia	1
Tyrosinemia	1

* Disorder has genetic heterogeneity but appears to follow an autosomal recessive pattern.

Table III

Indications for Genetic Counseling from Pedigree Data:

X-Linked Traits

Hemophilia A, classic hemophilia	1
Muscular Dystrophy, Duchenne type	1

Table IV

Indications for Genetic Counseling from Pedigree Data:

Chromosomal Anomalies

Deletion syndrome	1
Down Syndrome	14
Edwards Syndrome	1
Inversion	1
*"multiple congenital abnormalities"	1

* consistent with a chromosomal anomaly

Table V

Indications for Genetic Counseling from Pedigree Data:

Multifactorial Inheritance

Anencephaly	3
Cardiac Defect	6
Cerebral Palsy	1
Cleft Lip	3
Cleft Palate	2
Clubfoot	3
Congenital Hip Displacement	1
Detached Retina	1
Diabetes	7
Epilepsy	4
Fetal Alcohol Syndrome	2
"Hypertrophic Organs"	1
Infertility	1
Lupus	2
Meningomyelocele	1
Neural Tube Defect (Unspecified)	3
Parkinson's Disease	2
Pyloric Stenosis	1
Schizophrenia	7
Spina Bifida	3

Table V Continued

Tetralogy of Fallot	1
Tracheo-Esophageal Atresia	2

Table VI

Indications for Genetic Counseling from Pedigree Data:

Potential Teratogenic Exposure

Anoril	1
DES	2
Phenobarbital	1
Prednisone	1
X-Rays	1

Table VII

Indications for Genetic Counseling from Pedigree Data: Miscellaneous

Abnormal Vascular Growth	1
Adoption	3
Alcoholism	12
Bicornate Uterus	1
"Congenital Lockjaw"	1
Consanguinity	3
Mental Disease, Unspecified	2
Mental Retardation	24
Spontaneous Abortion	17

Table VIII

Indications for Genetic Counseling from Pedigree Data:

Cancer

Bladder	2
Bone	1
Brain	7
Breast	9
Cervical	1
Colo-rectal	10
Leukemia	1
Liver	5
Lung	4
Lymphoma	1
Prostrate	3
Skin	2
Stomach	5
Throat	4
Uterine	3
Unspecified Type	11

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