INTERNATIONAL FETAL SURGERY REPORT: ANNUAL REPORT, 1984.

INTRODUCTION:

In June of 1982 a clinical workship for discussion of methods and results of in utero fetal surgical procedures was held in Santa Ynez, California under the sponsorship of the KROC Foundation. At the conclusion of this meeting it was decided to attempt to establish an international registry to record all cases of surgical therapy for fetal obstructive uropathy and hydrocephalus. By election, the registry was placed at the University of Manitoba, Winnipeg, Manitoba, Canada. Details of discussion and recommendations including the establishment of the registry and the address have been previously published. In 1983 the initial report of the registry data was given at the fetal surgery meeting held in June, 1983 in Aspen, Colorado under the sponsorship of the National Foundation - March of Dimes. In this present report the registry data as compiled to May of 1984 are presented.

Method of Data Collection and Analysis:

Case entry to the registry is strictly voluntary. The availability of the registry and details for submission are widely published. In addition to submission by this route, the registrar also undertook to contact centers in the U.S.A., Europe, South America, Australia and New Zealand to enquire if such surgery was ongoing or contemplated and to arouse interest in participation in the registry. An ongoing literature review was established and all centers reporting cases of fetal surgical intervention not included in the registry were contacted and participation requested. Whenever relavant contact was established a detailed review of the case history(s) in question was requested.

Case data received was stored on computer compatible forms for data analysis. Because of the diversity of clinical data for each case the cummulative results are presented without statistical analysis. The reader is reminded that case selection is neither random nor complete and therefore may exhibit selection bias. Further, since the registry does not include entry of non-treated controls the effect of therapy or the natural history of the disorder cannot be determined from these data.

Results:

A) Logistics and Background Data of Registry Function:

Thirty-one centers in the western world were contacted; 15 of these centers contributed case material to the Registry. Eight responding centers were in the U.S.A., three in Canada, two in Great Britain, and one each in Australia and Israel and one in Chile. Sixty-three requests in writing, or by direct contact were received requesting the most recent update of the Registry data and in each instance such data was forwarded. All but one of these requests originated from the U.S.A. (54 requests) or Canada (8 requests).

B) Registry Data:

1. Obstructive Uropathy:

In total 52 cases of fetal obstructive uropathy treated by in utero chronic placement of a vesico-amniotic shunt are reported. Reported cases originated from six countries: 23 cases were reported from Great Britain, 18 cases from the United States of America, 7 cases from Canada, 2 cases from Chile and 1 case each from Israel and Australia. The number of cases per center ranged from 1 to 20 cases. Thirteen of 15 centers reported one case only, 3 centers reported 2 cases, 1 center reported 5 cases, 1 center reported 8 cases and the remaining center reported 20 cases. In 3 of 52 cases the shunt was placed in a single attempt, in 11 cases two attempts were required, in 3 cases three attempts, in two cases 4 attempts, and in 1 case more than 5 attempts occurred. In 2 cases the number of attempts before successful shunt placement was not given.

a) Survival Statistics: In total 23 of 52 cases (44.2%) survived for at least the neonatal period (28 days) and to as long as four years after treatment. 29 perinates died, of which 6 were stillbirths and 23 were neonatal deaths (Table 1). Two of the stillbirths were the result of late second trimester abortion (< 22 weeks) for either associated chromosomal anomaly (Trisomy 13) determined subsequent to shunt placement or due to failure to detect renal function after shunt placement. Two stillbirths occurred more than six weeks after shunt placement, being the result of "cord entanglement" in one instance and associated with major CNS anomaly in the other instance. The remaining two stillbirths occurred within one week of shunt placement; in both premature labour ensued within 4 days of treatment and intrapartum fetal death occurred. In one instance a diagnosis of acute chorioamnionitis was confirmed. Thus in at least two of the six stillbirths and in two of the 29 total deaths, procedure associated complications may have contributed to the perinatal deaths. 23 infants died in the neonatal period, all within the first three days of life and most (21 of 23) within the first few hours of life. 20 of the 23 (87%) neonatal deaths were due to inability to establish ventilation due to suspect or proven pulmonary hypoplasia, 2 were due to associated multiple anomalies (8.7%) and one was due to absent renal function (4.30%) (Table II). Considering total deaths, 20 of 29 were due to pulmonary hypoplasia, three were due to associated anomalies, two were a probable result of treatment complication, two were unexplained, and one was due to renal failure (Table I).

b) Factors Affecting Survival:

i) Diagnosis at delivery (Table II)

In 29 of 52 cases (56%) the etiology of the obstructive uropathy was either unproven (e.g. suspected posterior urethral valves) or unknown; in 10 of these 29 cases the fetus survived (34.5%). In 12 cases, all male infants, a diagnosis of obstruction due to posterior urethral valve was made (23%); 11 of these 12 fetuses survived (91.6%). Six of 52 (11.5%) cases exhibited multiple anomalies in association with obstructive uropathy; none survived (0%). In two cases (3.8%), both male, a diagnosis of "Prunebelly Syndrome" was made; both survived (100%). In two cases (3.8%), both female, a diagnosis of urethral atresia was made, neither survived (0%). In the remaining case (1.9%) the diagnosis was bilateral multicystic kidneys; the infant survived.

ii) Gestational Age at diagnosis and treatment, and duration of treatment (Table 3 and 4)

No obvious relationship between the gestational age at the time of diagnosis and subsequent outcome was apparent, survival ranging from 30% when the diagnosis was made between 20 to 24 weeks and 100% when made between 26 and 28 weeks (Table 3). Similarly no relationship between gestational age and treatment and outcome was apparent, survival ranging from 0% with treatment at 22-24 weeks to 86% with treatment between 26 to 28 weeks (Table 3). Therefore earlier diagnosis and treatment did not appear to increase the probability of survival. The interval between diagnosis and treatment was not related to survival (Table 4). The relationship between the

duration of treatment and survival is unclear but may indicate survival is better when the duration of treatment is at least two weeks (Table 4).

The presence of oligohydramnios determined by subjective assessment of amniotic fluid during ultrasound scanning was not related to survival (Table 5). In 37 of 52 (71.1%) cases oligohydramnios was present and 15 of these 37 infants survived (40.5%). In contrast 14 of 52 fetuses (26.9%) were reported to have normal amniotic fluid volume; 6 of these fetuses survived (42.8%). Similarly no clear relationship between the presence or absence of associated hydroureter/hydronephrosis and survival was recognized (Table 5).

2. Obstructive Hydrocephalus:

To date reports of 28 fetuses with obstructive hydrocephalus treated in utero have been entered into the registry. Twenty-six of these 28 fetuses were treated by chronic placement of a ventriculo-amniotic shunt; the remaining two fetuses were treated by serial ventriculocentesis (>3). Treated cases were referred from seven centers, all in the United States of America. The maximum number of cases treated in any one center was five.

Outcome:

Twenty-three of 28 fetuses survived after treatment (82.1%) and five fetuses died during treatment (1 case) or within 2 months after delivery. Two of these deaths may be considered a direct result of treatment; in one instance fetal death occurred during shunt placement, the other death, due to prematurity resulted from premature labour with suspect chorioamnionitis developing within 48 hours of shunt placement. Two deaths were a direct result of associated major anomalies and the etiology of the remaining death was not ascertained.

The diagnosis features associated with obstructive hydrocephalus are listed in Table 6. Seventeen of 28 fetuses had suspect or proven aqueduct stenosis (60.7%), four fetuses had multiple anomalies (14.3%), two fetuses had holoprosencephaly (7.1%), one fetus had lumbar myelomengocoele and associated Arnold-Chiari Syndrome (3.6%), one fetus had a Dandy-Walker Syndrome (3.6%) and in the three remaining fetuses the etiology of the defect was not classified (10.7%). The relationship between the primary diagnosis and survival morbidity is listed in Table 6.

Eleven fetuses were normal at follow-up (range 1-18 months, mean 8.1 ± 6 SD months) representing 39.3% of all treated fetuses and 47.8% of surviving fetuses (11 of 23). Two fetuses exhibited mild neurological handicap evident at 10 months reporting 7.2% of all patients and 8.7% of survivors. Three fetuses exhibited moderate handicap and follow-up (range 4-18 months), representing 10.7% of all patients and 13% of survivors. Seven fetuses exhibited severe handicap at follow-up (range 3-18 months, mean 8 ± 6.3 months) representing 38.6% of all patients and 34.8% of survivors.

The diagnosis at the time of initial diagnosis of hydrocepahlus ranged from 22 to 30 weeks with a mean gestation of 25.7 ± 2 weeks (SD). The gestational age at the time of diagnosis was not related to survival or handicap (Table 7). The gestational age at the time of treatment ranged from 23 to 33 weeks (mean 27 ± 2.9 weeks) and was not related to survival or handicap (Table 7). The duration of treatment ranged from less than one week to as long as 16 weeks (mean 7.44 ± 4.4 weeks). All deaths (N=5) occurred within a four week period after treatment (Table 7). Intact survival did not appear to increase as the duration of treatment increased.

Associated anomalies in treated cases included facial cleft with associated pulmonary hypoplasia (1 case), arthrogryphosis multiplex congenita (1 case), diaphragmatic hernia (1 case), multiple anomalies of cardiac, G.I., and pulmonary systems (1 case), holoprosencepahly (2 cases), and Down's Syndrome (1 case). The overall incidence of associated anomalies was 25% (7 of 28 cases). Serious morbidity among all survivors included seizure disorders (2 cases), cortical blindness (2 cases), mild paresis of lower limb (1 case), and severe connative/motor retardation in eight cases.

DISCUSSION:

The International Fetal Surgery Registry has been in existance since June of 1982. During this two year span, a total of 80 cases, 52 of obstructive uropathy and 28 of obstructive hydrocephalus have been entered. The data reported from the Registry may not be without bias since data reporting was voluntary and therefore the potential for reporting of successful outcome only exists. While such a bias may always exist within a voluntary registry it is encouraging to note that data reported from centers with similar cases appears to be consistent within the overall data base. This observation suggests but does not prove that a representative sample has been obtained. The difficulty is convincing individuals to submit data has, and no doubt will continue to exist. Nonetheless it is encouraging to note the sample size for a very new area of treatment is as large as it is and that reports continue to come in to the Registry.

The data for both fetal disease processes suggest that treatment may be of benefit. The reader is recommended however that matched non-treated controls are not available for comparison so whereas the positive effect of treatment appears clear, the magnitude of such change remains undetermined. The great need for prospective reporting of control cases is obvious. It is also clear that the beneficial effect of treatment is not without risk for the fetus and at least potential risk for the mother. Four fetuses, (two in each group) died as a direct complication of their treatment (5%), a risk similar to that seen at the time of intrauterine transfusion. Major associated anomalies remain a concern in deciding about treatment; in

the group in total 8 of 80 infants (10%) had associated anomalies which in retrospect would have negated treatment attempts. The question of morbidity among survivers also remains a major question. With obstructive uropathy distribution of outcome approach an all or none position with early death or relatively normal low morbidity outcome the rule. In contrast survival is better with obstructive hydrocepahlus, but serious neurological morbidity remains a serious complication.

It seems evident from these data that there is rational basis for implementation of in utero treatment for obstructive uropathy and hydrocephalus. A great deal more information most be gathered, including data on the natural hsitory of these disease processes before this evolving innovative therapeutic approach can become an accepted part of prenatal care.

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TABLE 1

Perinatal Death by Time and Etiology in 52 treated cases of Fetal Obstructive Uropathy (N=29)

Etiology	Time of Death: Stillbirth	Neonatal Death	Total	% Total Deaths
Associated Anomaly	2	2	4	13.8%
Unexplained	1	0	1	3.40%
Procedure Complication	2	0	2	6.90%
Pulmonary Hypoplasia	0	20	20	69.0%
Renal Failure	1	1	2	6.90%
Total	6	23	29	100%

TABLE 2

Outcome in 52 cases of Treated Fetal Uropathy: Association Between Primary Diagnosis and Survival

Primary Diagnosis	No. of Cases	% total cases	Sex	No. of Survivors	% Survival Per Diagnosis	% of Total Survivors	
Unknown or unproven	29	55.8%	100% ♂	9	34.5%		39.1%
Posterior urethral valves	12	23%	100% ♂	11	(91.6%)		47.8%
Associated anomalies	6	11.5%	Not known	0	0%	0%	0%
Urethral atresia	2	3.9%	100% ♀	0	0%	0%	
"Prune belly" Syndrome	2	3.9%	100% ♂	2	100%	2 of 23	8.7%
Multicystic kidney	1	1.90%	♂	1	100%	1 of 23	4.4%
Total	52	100%	95% ♂	23	-	44.2%	-

TABLE 3

Relationship of Gestational Age at Diagnosis and Treatment to Outcome

Gestational Age	At Diagnosis			At Treatment		
	No.	Survivor	% Survival	No	Survivors	% Survival
<20 weeks	15	6	40%	11	3	27.3%
>20 <22	5	2	40%	3	2	66.6%
>22 <24	10	3	30%	8	0	0%
>24 <26	7	2	28.6%	8	2	25%
>26 <28	4	4	100%	7	6	86%
>28 <30	2	1	50%	5	4	80%
>30 <32	4	3	75%	5	4	80%
>32	5	2	40%	5	2	40%
Total	52	23	44.2%	52	23	44.2%

TABLE 4

Interval Between Diagnosis and Treatment, at Treatment to Delivery: Relationship to Survival

No. of weeks	Interval Dx to Tx			Tx to Delivery (duration of treatment)		
	No.	Survivor	% Survival	No.	Survivor	% Survivor
<1 week	28	11	39.3%	10	0	0%
1 - 2 weeks	12	7	58.3%	17	10	58.8%
3 - 4 weeks	6	2	33.3			
5 - 6 weeks	3	1	33.3%			
6 - 10 weeks	3	2	66.6%	11	6	54.5%
>10 weeks*	-	-		14	7	50%

*longest duration 18 weeks.

TABLE 5

Associated Ultrasound Findings and Survival

Associated Finding	No. of Cases	% total Cases	No. Survivors	% Survival
Oligohydramnios	37	71.1%	15	40.6%
Normal Amniotic Fluid Volume	14	27%	6	42.3%
Amniotic Fluid Volume Unknown	1	1.9	1	100%
Hydronephrosis Present	43	82.7%	19	44.2%
Hydronephrosis Absent	7	13.4%	3	42.8%
Unknown	2	3.9%	1	50%

TABLE 6

OBSTRUCTIVE HYDROCEPHALUS: Outcome by Primary Diagnosis

		OUTCOME				
Primary Diagnosis	Total Cases	Normal	Mild Handicap	Moderate Handicap	Severe Handicap	Dead
Aqueduct Stenosis	17	9 (52%)	1 (6%)	2 (12%)	3 (18%)	2 (12%)
Multiple Anomalies	4	0	0	0	3 (75%)	1 (25%)
Holoprosencephaly	2	0	0	0	1 (50%)	1 (50%)
Dandy-Walker	1	1	-	-	-	-
Arnold-Chiari	1		1	-	-	0
Unknown Etiology	3	1 (33.3%)	-	-	1 (33.3%)	1 (33.3%)
Total	28	11 (39.3%)	2 (7.2%)	2 (7.2%)	8 (28.6%)	5 (17.7%)

TABLE 7

OBSTRUCTIVE HYDROCEPAHLUS: Duration of Treatment and Outcome

Duration of Treatment (weeks)	Total	Outcome									
		Normal		Mild Handicap		Mod. Handicap		Severe Handicap		Dead	
		No	%	No	%	No	%	No	%	No	%
0-2 weeks	3	0	0	0	0	0	0	0	0	3	100%
>2-4 weeks	5	2	40	1	20	0	0	0	0	2	40%
>4-8 weeks	9	5	55.5	0	0	1	11.1	3	33.3	0	-
>8-16 weeks	11	4	36	1	9	1	19	5	36		
TOTAL	28	11	39.3	2	7.1	2	10.9	8	25	5	17.8