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Efficacy of the High Dose Mitomycin-C Intrabifurcation of Aorta Infusion for Treatment of Squamous Cell Carcinoma of Cervix Stage II B - III B

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Abstract : *The neoadjuvant single high dose chemotherapy for induction the high clinical complete regression with low toxicities, following by radical hysterectomy and pelvic lymphadenectomy produced high pathological complete regression and favourable survival time. This procedure was used instead of standard radiotherapy in treatment of squamous cell carcinoma of the uterine cervix stage II B -III B who refused the radiation treatment.*

The intrabifurcation of aorta by Mitomycin-C 35 mg/m2 single infusion was performed in 36 new cases, revealed the clinical complete regression 86.1% and partial regression 5.6% after chemotherapy 4-6 weeks. Twenty eight patients with clinical complete regression were treated by radical hysterectomy and pelvic nodes dissection, which showed pathological complete regression in 39.3%, small residual cancer in the cervix encountered in 39.3% and residual cancer in the cervix and/or positive pelvic nodes accounted for 21.4%. The bone marrow was moderately depressed in the second week after treatment but experiencing tolerable non-haematolgic toxic effects.

The recurrence rate occured 25.0% after radical surgery and oral chemotherapy. The over all 5-years survival rate was 75.0%. The follow up period until August 1992 showed that the survival time ranged from 6.5-101.5 months (median 93.5 months). The 5-years survival rate of the pathological complete regression group was 100.0%, and 88.2% for the residual cancer group. (Thai J Obstet Gynaecol 1994;6:1-6.)

Key words : intrabifurcation of aorta infusion, mitomycin-C, squamous cell carcinoma, radical hysterectomy

Short title : Mitomycin-C for cervical cancer stage II-III

The cervical cancer is the first most common gynaeclogic cancer, during 1980-1989 our department had the incidence of the cervical cancer 73% of the female genital cancer, approximately 57% of the patients fall into stage III-IV,[1] and the treatment should be radiation therapy. The numerous patients of this group were treated by herb or superstitions, instead of radiation therapy, thus had no chance of survival. The other alternative treatment such as neoadjuvant chemotherapy with surgery should be useful for these cases. The use of Mitomycin-C in treatment of advanced cervical cancer showed response rate of 22-85%.[2-6] The previous trial intravenous high dose Mitomycin-C in treatment of the cervical cancer stage II-III revealed the clinical complete regression 16% and partial regression 68%, with high incidence of toxicities.[7] The objective of this study was to find out the other model neoadjuvant chemotherapy with low incidence of toxicities, while producing the high clinical and pathological complete regression with favourable survival. The neoadjuvant single high dose Mitomycin-C intrabifurcation of aorta by infusion was performed in this trial.

Materials and Methods

The patients eligibility for study included the pathological finding of squamous cell carcinoma stage II B - III B, who refused of radiotherapy during March 1984 - February 1986. The size of the lesion should be measurable, having never been treated by other chemotherapy, and no medical or psychological disease which contraindicate for radical surgery. Patients were required to have adequate bone marrow function (a leukocyte count greater than 400/Cu.mm., a platelet count greater than 100,000/Cu.mm., haemoglobin level greater than 8 gm/100 ml., normal liver function (serum SGOT level more than 100 sigma unit, normal renal function (serum creatinine level less than 2 mg/100 ml.), and signed the consent form.

A single dosage of Mitomycin-C 35 mg/m2 was given intrabifurcation of aorta infusion over 5 minutes under fluorography with compression the femoral arteries just below the point of puncture. The patient was admitted in hospital at least 12 hours for observation of complication. Nausea and vomiting were treated by metoclopamide 10 mg. subcutaneously or intravenously every 4-6 hours.

The follow up included weekly physical examination, complete blood count, and non-haematologic toxicities observation. The evaluation of response was performed 4-6 weeks after medication. The clinical complete regression was defined as disappearance of lesion in the cervix, vaginal fornices and parametrium. Partial regression was defined as a decrease of lesion at least 50%. Decreasing of lesion less than 50% was defined as no regression.

The patients with complete

regression were treated by radical hysterectomy and pelvic lymph node dissection. The patient who had no residual cancer in the surgical specimen, was defined as the pathological complete regression, was treated postoperatively by oral Mitomycin-C 2 mg/day for 7 days in every 4 weeks for 6 cycles. The patient who had residual cancer in the cervix was treated postoperatively by the same dosage of the oral Mitomycin-C. The group of residual cancer in the cervix and/or positive cancer in the pelvic lymph nodes was treated by external radiation 5000 cGy.

Results

During March 1984-February 1986, 36 patients included in this trial, age ranged were 25-61 years (mean 44.8 ± 9.2). The majority of cases fell in 40-49 years old. The stage II B disease 28 cases age ranged between 26-61 years (mean 43.9 ± 8.3) and stage III B 8 cases age ranged between 25-60 years. (mean 47.8 ± 11.9)

Among 28 patients in stage II B, showed clinical complete regression 92.9%. The stage III B 8 patients have clinical complete regression

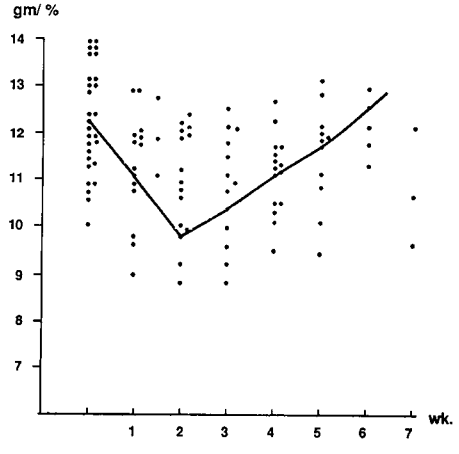

Fig. 1 Haemoglobin levels after mitomycin-C

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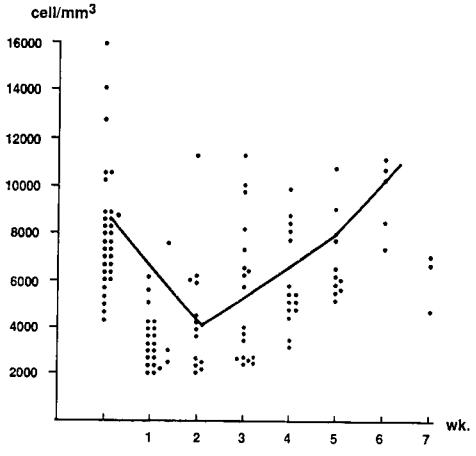

Fig. 2 Leucocyte count levels after mitomycin-C

Fig. 2 Leucocyte count levels after Mitomycin-C

Table 1 ***Clinical response after Mitomycin-C infusion***

Stages	No.of patients	Response (%)		
		Complete regression	Partial regression	No regression
II	28	26 (92.9)	-	2 (7.11)
III	8	5 (62.5)	2 (25.0)	1 (12.5)
Total	36	31 (86.1)	2 (5.6)	3 (8.3)

Table 2 *Pathological finding after radical hysterectomy and pelvic lymphadenectomy in 28 cases of clinical complete regression*

Pathology report	Stage II	Stage III	Percentage (%)
No residual cancer	10	1	11 (39.3)
Residual cancer in cervix	10	1	11 (39.3)
Residual cancer in cervix and/or pelvic lymph nodes	5	1	6 (21.4)
Total	25	3	28

Table 3 *Recurrence after radical hysterectomy and pelvic lymphadenectomy in 28 cases of clinical complete regression group*

Stage	Pathological finding			Total
	Pathological Complete regression	Residual cancer in cervix	Residual cancer in cervix and or nodes	
II B	2	2	2	6
III B	-	-	1	1
	2	2	3	7

62.5%, and partial regression 25.0%. All of them have clinical complete regression 86.1%, and partial regression 5.6%. (Table 1)

The drug toxicity revealed moderate degree of marrow suppression at the end of the second week (Fig. 1,2). Two patients have leukocyte count grade 2 and 3, and spontaneously increased to the normal level in 4 weeks. The non-haematologic toxic effects revealed nausea-vomiting grade 2 69.44%, alopecia grade 2 47.22%, and blue nail 25.0%.

The radical hysterectomy and pelvic lymphadenectomy were performed in 28 patients of clinical complete regression group and revealed the pathological complete regression 39.1%, small residual cancer in the cervix 39.1%, small residual cancer in the cervix and/or positive pelvic lymph nodes 21.4% (Table 2). Three patients of clinical complete regression refused surgery, were treated by oral Mitomycin-C. One of them was alive without disease with survival time 101 months, 2 patients showed central recurrence or left supraclavicular node metastases within 7, 12 months and expired with survival time 12, 17 months.

The partial regression group was treated by oral Mitomycin-C, expired with survival time 6.5 and 8.0 months. No regression 3 cases, one

was treated by oral Mitomycin-C and two refused further treatment and expire with survival time 10, 8 and 7 months.

Seven of 28 patients (25.0%) in clinical complete regression group showed recurrence or distant metastases after radical surgery 9.0-37.0 months (Table 3). All of them were treated by external radiation or Bleomycin plus Mitomycin-C. Two of this group expired with survival time 22.5 and 27.5 months.

The over all 5-years survival was 27 out of 36 cases (75.0 %). The follow up was performed until August 1992, revealed survival time 6.5-101.5 months, median survival 93.5 months. The 5-years survival of the pathological complete regression was 100.0 %, and 88.2 % for the group of residual cancer in the cervix and or positive pelvic lymph nodes.

Discussion

The effectiveness of Mitomycin-C in treatment of the cervical cancer should be high dosage,[2-6] but not more than 40 mg/m2.[8] The multiple high dosage showed severe toxicities either haematologic or non-haematologic effect.[7] The single high dose intrabifurcation of arota infusion have the high concentration of drug in the pelvic organ especially cervix, uterus, pelvic wall including pelvic nodes. Thus we can increase the clinical complete regression to 86.1% comparing with our previous trial 16.0 %,[7] followed by a chance of radical surgery. Only the single infusion of chemotherapy in this trial induced the low and tolerable toxicities. Although the recurrence was found 25.0 % of cases post radical surgery and oral chemotherapy, we can treat with radiation or chemotherapy, unfortunately 2 patients did not response. In the future we can increase the oral Mitomycin-C to 3 mg/day for 7 days in combination with oral 5-Fluorouracil 300 mg/day for 7 days, however this recurrent rate may be decrease.

Conclusion

This procedure is the other alternative treatment for the patient of cancer stage II-III, who refused the standard radiation and we can preserve the ovarian function in young women. The 5-years survival of the patients after radical surgery reached 92.9 %, especially 100 % in the pathological complete regression group, and 88.2 % of the residual cancer group.

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Borderline and Malignant Epithelial Ovarian Carcinoma At Maharaj Nakorn Chiang Mai Hospital: A Retrospective Study of Epidemiology and Basic Charateristics

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Abstract : *This study reported on 324 cases of borderline and malignant common epithelial tumours treated at Maharaj Nakorn Chiang Mai Hospital over a nine-year period from 1984-1992. The mean age of patients was 48.8 ± 13.3. Most common presenting symptoms were abdominal pain or abdominal mass and 54.3% of the patients were diagnosed in the advanced stage. Mucinous tumuor was the most common cell type (35%), but serous and endometrioid (60%) carcinoma were found in the more advanced stage and had a higher incidence of bilaterality and a higher incidence of ascites than other cell types. (Thai J Obstet Gynaecol 1994; 6: 7-15)*

Key words : ovarian carcinoma, epithelial tumors, epidemiology

Ovarian cancer which appears to be increasing in incidence, presents one of the most frustating problems in gynecology. In the United States, this disease is the sixth most common female cancer[1-3], the fourth most common cause of female cancer death[2] and the leading cause of gynecologic cancer death, accounting for 52% of all deaths due to gynaecologic malignancy[2,4].

Concerning gynaecology, ovarian cancer is the second most common cancer after cervical cancer in Thailand[5-7]. Regarding histological type, common epithelial cancer account for 80-90% of all ovarian cancer in Western countries[8-9], while comprising 70-76% in Japan[10]. The epidemiology and distribution of histological type of ovarian cancer varies from one ethnic group to another. Few information is available regarding epithelial ovarian carcinoma for nor-

therners in Thailand, hence, the objective of this study was to report on the epidemiology, the clinical characteristics, the distribution of histological type and stage of the diseases of borderline and malignant common epithelial tumours at Maharaj Nakorn Chiang Mai Hospital over a nine-year period.

Materials and Methods

This study comprises all cases of primary epithelial ovarian cancer treated at Maharaj Nakorn Chiang Mai Hospital between January 1984 and December 1992. All patients had exploratory laparotomy with histologically proven epithelial carcinoma and were classified according to WHO classification[11] and FIGO staging (1987) of ovarian cancer[12].

Information was collected from medical records and questionnaires recorded by the social worker who were responsible for the gynaecological cancer registry.

In the nine year-period, there were 433 new cases of primary ovarian cancer. Of these, 324 cases diagnosed as borderline or malignant epithelial tumours were analysed in this study.

Results

During the period of study, 5040 cases of gynaecologic canacer were registered. Ovarian cancer was the second most common gynaecologic cancer accouning for 433 cases or 8.6% of primary genital cancer.

Common epithelial tumour was the most common type, comprising 74.8% (324 cases) of all ovarian cancer. The rest were germ cell tumors, sex cord stromal tumours and unclassified type which accounted for 17.8% (77 cases), 6.2% (27 cases) and 1.2% (5 cases) respectively.

Of the 324 cases of borderline and malignant epithelial tumours studied, almost all patients (321 cases or 99.1%) were from different provinces in the Northern part of Thailand and 40.4% (131 cases) were from Chiang Mai province. However, only 49.1% (159 cases) were operated on at Maharaj Nakorn Chiang Mai Hospital, and 50.9% (165 cases) were operated on at other hospitals prior to referral to our hospital for further treatment after definite diagnosis.

The age distribution of the patients ranged from 15-82 years with the mean age of 48.8 ± 13.3 years. More than half of the cases (52.2%) were between 40-60 years and 49.4% were in the post menopausal stage. Most of the patients (82.4%) were married and 25.6% were nulliparous. Determining the occupation of the patients, about 34% were agricultural workers and 20% were laborers. (Table 1)

Most patients presented with abdominal mass or abdominal pain (87%), only 3.1% presented with abnormal vaginal bleeding and 6.1% had no symptom and were diagnosed during their annual check up. Other less common symptoms were diffi-

Table 1 *Characteristics of the patients (n=324)*

Characteristic		Number	Percent
Age (year)			
	10-19	5	1.5
	20-29	24	7.4
	30-39	54	16.7
	40-49	70	21.6
	50-59	99	30.6
	60-69	57	17.6
	70-79	14	4.3
	80-89	1	0.3
	Mean age±SD=48.8±13.3	Range 15-82 years	
Menopause			
	Yes	160	49.4
	No	164	50.6
Marital Status			
	Single	47	14.5
	Married	267	82.4
	Not stated	10	3.1
Parity			
	0	83	25.6
	1-2	95	29.4
	3-4	56	17.3
	5-6	38	11.7
	7-8	23	7.1
	9-10	11	3.4
	>10	8	2.4
	No data	10	3.1
	Mean parity±SD=2.91±2.97	Range 0-14	
Occupation			
	Agriculturer	110	33.9
	Labourer	67	20.7
	Merchant	42	13.0
	Housewife	23	7.1
	Government officer	19	5.9
	Dependent (Children, elderly)	63	19.4

Table 2 *Main symptoms of the patients*

Main Symptom	Number	Percent
Abdominal mass	152	46.9
Abdominal pain	130	40.1
Abnormal vaginal bleeding	10	3.1
Others	6	1.9
No symptom (check up)	6	1.9
No datum	20	6.1
Total	324	100.0

Others: difficulty in urination, enlargement of supraclavicular lymph node, weakness.

Table 3 *Distribution of histological type of tumours*

Histological Type	Borderline Number	%	Malignant Number	%
Serous	4	16.7	90	30.0
Mucinous	20	83.3	105	35.0
Endometrioid	-	-	40	13.3
Clear cell	-	-	17	5.7
Brenner	-	-	1	0.3
Mixed type	-	-	8	2.7
Adenocarcinoma (not defined)	-	-	39	13.0
All	24	100.0	300	100.0

culty in urination, enlargement of supraclavicular lypmh node or weakness. (Table 2)

Among the malignant tumours, mucinous tumour was the most common histological type (35.0%). Serous tumour and endometrioid tumour ranked the second and the third respectively, (30.0% and 13.3%). Of all cases studied, borderline tumour accounted for 7.4% and mucinous tumour was also the most common type in the borderline group (83.3%). (Table 3)

More than half of the patients (54.3% or 163 cases) were admitted in advanced stage (Stage III or IV) and only 33.3% (100 cases) were in stage I. If histological type was considered, percentage of the patients in stage I with clear cell and mucinous carcinoma tended to be higher than those of serous and endometrioid carcinoma. Therefore, the percentage of patients in the advanced stage appeared to be higher in endometrioid and serous carcinoma than those of other types. However, all patients with borderline tumours were stage I. (Table 4)

Table 5 shows that malignant

Table 4 *Stage of diseases by histological type*

Histological Type		Stage of Disease (%)				
		I	II	III	IV	Unknown
Serous carcinoma	(n=90)	31.1	8.9	50.0	5.6	4.4
Mucinous carcinoma	(n=105)	40.9	2.9	44.8	7.6	3.8
Endometrioid carcinoma	(n=40)	25.0	12.5	47.5	12.5	2.5
Clear cell carcinoma	(n=17)	41.2	23.5	23.5	-	11.8
All malignant tumours	(n=300)	33.3	7.7	46.0	8.3	4.7
All benign tumours	(n=24)	100.0	-	-	-	-

common epithelial tumours had the mean age of 49.0 ± 13.1 years which tended to be a little higher than 45.7 ± 15.6 of borderline groups. In addition, the higher the stage of the disease, the older the mean age of the patient. In the malignant tumour group, mucinous and clear cell tumours appeared to be found in the younger age group (mean age 44.7 ± 13.5, 44.5 ± 13.0) compared to serous and endometrioid tumours (50.0 ± 12.1, 52.7 ± 10.9)

Ascites tended to be more common in more advanced stages of the diseases. Endometrioid carcinoma seemed to be associated with ascites more frequently than any other cell type (57.5%), while clear cell carcinoma presented with ascites in only 29.4%. (Table 5)

In malignant tumours, ovaries were bilaterally involved in 34% and the right ovary seemed to be more frequently involved than the left. Bilateral involvement in stage I was 11.0% and appeared to be higher in the more advanced stage. Endometrioid and serous carcinoma involved both ovaries more frequently than either clear cell or mucinous carcinoma. In all cell type except for endometrioid carcinoma, the right ovary seemed to be involved more commonly than the left ovary. With regard to the borderline tumours, bilaterality was found in 8.3% and the left ovary appeared to be involved more common than the right one. (Table 5)

Table 5 also shows that there was no difference in the size of the tumour compared by stage but considering histological type mucinous tumours appeared to be larger in size. The mean size of tumours in the malignant group was smaller than that of borderline group (15.1 ±6.7 versus 19.5 ± 10.4)

Discussion

The incidence of ovarian cancer varies from one ethnic group to another[4]. In developed countries, ovarian cancer is the second most common gynaecologic malignancy after endometrial cancer, comprising about 26% of all gynaecologic cancer[4]. This cancer is also the second

Table 5 ***Mean age of the patient, Presence of malignant ascite, Laterality of ovary involved and mean size of ovarian tumour in different group***

Characteristic	Stage of Malignant Tumour				Histological Type					
	I	II	III	IV	Serous Ca.	Mucinous Ca.	Endometrioid Ca.	Clear cell Ca.	All malignant tumours	All borderline tumours
	(n=100)	(n=23)	(n=138)	(n=25)	(n=90)	(n=105)	(n=40)	(n=17)	(n=300)	(n=24)
Mean Age Of The Patient (years)										
Mean ± SD	45.7 ± 13.9	45.7 ± 11.5	50.5 ± 12.8	53.0+-9.1	50.0 ± 12.1	44.7 ± 13.5	52.7 ± 10.9	44.5 ± 13.0	49.0 ± 13.1	45.7 ± 15.6
Range	18-82	26-69	15-78	34-67	25-82	15-74	27-75	15-66	15-82	17-77
Presence Of Malignat Ascite (%)										
No	64.0	56.5	15.9	8.0	35.5	34.3	27.5	58.8	35.0	79.2
Yes	27.0	30.4	60.9	68.0	47.8	40.9	57.5	29.4	45.7	20.8
No Datum	9.0	13.1	23.2	24.0	16.7	24.8	15.0	11.8	19.3	-
Laterality Of Ovary Involved (%)										
Left	32.0	30.4	16.7	16.0	17.8	27.6	27.5	29.4	23.7	58.4
Right	51.1	17.4	24.6	16.0	26.7	41.9	25.0	41.2	32.0	33.3
Bilateral	11.0	43.5	50.0	48.0	41.1	22.9	45.0	23.5	34.0	8.3
No Datum	6.0	8.7	8.7	20.0	14.4	7.6	2.5	5.9	10.3	-
Mean Size Of Ovarian Tumour (cm.)										
Mean+-SD	15.4 ± 6.7	16.0 ± -6.0	14.6 ± 6.8	15.9 ± 7.6	13.5 ± 6.9	17.4 ± 6.4	12.8 ± 5.1	14.7 ± 5.9	15.1 ± 6.7	19.5 ± 10.4
Range	3-32	8-30	3-40	5-30	3-30	5-40	5-25	8-30	3-40	7.40

Unknown stage=14 cases

Other malignant histological type of 48 cases [Brenner 1 case, Mixed epithelial carcinoma 8 cases, Adenocarcinoma (not defined type) 39 cases.]

most common gynaecologic cancer encountered in Thailand but comprised only 7-12% of all gynaecologic cancer[5,6,13]. This may be attributed to the high incidence of cervical cancer in our country. At Maharaj Nakorn Chiang Mai Hospital, the ovarian cancer made up 8.6% of cancer in gynaecology compared to 81.6% of cervical cancer.

Common epithelial tumour was the most common type, accounting for 74.8% of all ovarian cancer cases which was lower than 80-90% reported form western countries[8,9], but was similar to 77.6% reported from Chulalongkorn Hospital[14], 67.4% from Ramathibodi Hospital[15] and 70-76% from Japan[10]. This might be related to a greater proportion of germ cell tumours in oriental women[4].

In this report, a mucinous carcinoma was the most frequent histological type, similar to the report from Srinagarind Hospital, Khon Kaen[16]; but quite different from studies of other countries and of the central part of Thailand which favored serous more than mucinous[8,10,14,15,17].

The mean age of patients with malignant common epithelial tumours was 49.0 ± 13.1 years. This is different from other reports which found these tumours in the older people[17,18]. We agree with Niruthisard S.[14] who stated that malignant epithelial tumours in Thailand are generally found in younger people than in western countries. Endometrioid carcinoma, though found in the older people than other types in this study, had a mean age of about 52 years compared to 57 years from another report[18].

With regard to borderline tumours; similar to many reports [10,14,15,17], mucinous tumour was the most common type. However, in this study the mean age was only about 3 years lower than the study of malignant tumours. But in other reports the age difference between the two groups were about 7-20 years [14,15,17].

Patients with malignant tumour in our study were diagnosed in the advanced stage in which 54.3% was a little lower than other reports.[4] This might be from incomplete surgical staging operation. The findings of the Ovarian Cancer Study Group[19] demonstrated that changes in stage occured in patients of stage I, II in about 33% when further investigations and reoperations for restaging were performed.

Serous and endometrioid carcinoma appeared to be diagnosed more frequently in the advanced stage (stage III of IV,) while clear cell carcinoma was diagnosed in the advanced stage of only 23.5%. The study of Auer et al[17] and of Niruthisard[14] also indicated that clear cell carcinoma tended to be discovered in the early stage.

In the present study, the incidence of ascites increased as the disease became more advanced and was more common in endometrioid and serous carcinoma (57.5%, 47.8%) comparing to 40.9% and 29.4% for mucinous and clear cell carcinoma,

respectively.

Bilaterality was found in 34% of all malignant patients. In stage I bilateral ovaries were involved in 11% and in advanced stage both ovaries were involed in 40-50%. Concerning histological type, bilaterality was more common in endometrioid and serous carcinoma (45.0%, 41.1%) as opposed to mucinous and clear cell carcinoma (22.9%, 23.5%) respectively. These findings were nearly the same as those reported from Chulalongkorn Hospital[14] which indicated bilaterality in serous, endometrioid, mucinous and clear cell were 40.1%, 34.4%, 12.9%, 18.8% respectively. With regard to borderline tumours, bilaterality was found in 8.3% compared to 7.7% reported by Niruthisard.

Although unexplained, our study demonstrated that malignant tumours (with the exception of endometrioid and borderline groups) had a predilection for the right ovary, which was also observed in other studies[14,15,20].

The high incidence of bilaterality and ascites in endometrioid and serous carcinoma may partly be attributed to more advanced stage at time of diagnosis.

Tumour size is usually larger in the mucinous group which is supported by the literature indicating that mucinous tumors may be fairly large[18], but the size was not quite the same in other histological types or among various stages. However, it was surprising that in this study, the mean size of borderline tumour appeared to be larger than the malignant group (19.5 ± 10.4 versus 15.1 ± 16.7). This may be attributed to the fact that mucinous tumour was found in a higher percentage (83.3%) of the borderline group compared to 35.0% in the malignant group.

This was a retrospective study and some information is incomplete especially those cases that had been operated on in other hospitals and sometimes the referral notes did not sometimes have the details of operative findings or exact stage of the disease. Hence this report may only demonstrate the trend of epidemiology, clinical characteristics, distribution of histological type and stage of borderline and malignant common epithelial tumours of the patients treated in our hospital which is a referral hospital for 17 provinces in the North of Thailand.

The main treatment for the ovarian cancer in our hospital is chemotherapy after cytoreductive surgery. The regimen of chemotherapy given was considered accounting to histological type, stage of diseases and also the socioeconomic status of the patients.

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Hypothesis

Is There a Link Between Stress, Beta-Endorphin and Diabetes Mellitus ?

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Beta-endorphin (beta-EP), neuropeptide cleaved from precursor pro-opiomelanocortin (POMC) under the control of Corticotropin Releasing Hormone (CRH), is generated in the CNS, hypothalamus and anterior pituitary, ovarian, testicular, thymic, pancreatic and placental tissues[1,2,3]. Production of beta-EP is extremely increased in stressful situations.

In the endocrine pancreas beta-EP containing cells are in close proximity to insulin containing ones. It has been confirmed that infusion of beta-EP caused a significant rise in plasma glucose concentration preceded by a significant increase in peripheral glucagon levels. Insulin responses to intravenous pulses of different glucose amounts were significantly reduced by beta-EP infusion. So, beta-EP stimulates glucagon inhibits basal and glucose-stimulated insulin secretion. Intravenous administration of small doses of beta-EP caused an immediate suppression of basal and glucose-stimulated insulin secretion. This effect was associated with a significant reduction of the glucose disappearance rates suggesting that the inhibition of insulin was of biological relevance.[4]

Beta-EPs are components of the intrapancreatic regulatory system which means beta-EP of pancreatic origin may function as paracrine or autocrine regulator of pancreatic islet cells[5]. The study performed in type-2 diabetes mellitus patients showed that infusion of human beta-EP produced significant and simultaneous increments in both insulin and glucagon concentration and decreased plasma glucose levels[6]. But, when the same diabetics were rendered euglycemic by an insulin infusion, beta-EP did not produce the expected decrease in plasma glucose concentration nor raise plasma insulin levels; only the response of glucagon was preserved. It is very important to stress on the fact that beta-EP at low dose levels inhibited and at high dose concentration augmented stimulated insulin secretion in experimental conditions, which supports the idea that a naloxone

sensitive beta-endorphin-binding component is present in pancreatic islets[7].

Having in mind that pregnancy is a diabetogenic factor in the very recent investigation, we confirmed that immunoreactive beta-EP in peripheral blood of pregnant women was found to increase with the progression of gestation, reaching maximal at term. This finding is particularly expressed in insulin dependent pregnant women. The cited study also confirmed that insulin caused a significant rise of beta-EP blood levels 1 hour after administration. Peripheral blood beta-EP levels did not significantly differ in insulin independent patients, in comparison with the healthy controls, while insulindependent one presented significantly higher levels. Inhibiting insulin secretion, beta-EPs are incorporated in the complex mechanism of gestational diabetes development[8].

In conclusion, there is a strong relationship between beta-EP rise caused by stress and diabetes mellitus.

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Prediction of Fetal Distress by Low Intra-amniotic Lysozyme Level

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Abstract : *Lysozyme activity was determined in amniotic fluid samples of 82 pregnant women at the end of gestation (37-40 wks). Forty eight specimens were from normal, while 34 were taken from high-risk pregnancies: Rh-alloimmunisastion, hydramnios, diabetes mellitus complicated by pregnancy-induced hypertension, diabetes mellitus with Rh-alloimmunisation, and Rh-alloimmunisation complicated by pregnancy-induced hypertension. Signs of fetal distress were present in 18 high-risk pregnancies. Lysozyme concentration in amniotic fluid was significantly lower in patients with signs of fetal distress, suffering from Rh-alloimmunisation[1-5], and diabetes mellitus with Rh-alloimmunisation [3]. Our data support the possibility of using the intraamniotic lysozyme level as a predictor of fetal distress. (Thai J Obstet Gynaecol 1994; 6:19-21.)*

Key words : lysozyme, amniotic fluid, fetal distress

Studies performed at the end of the first trimester confirmed that exocoelomic fluid is a transudate of the maternal serum. Amniotic and exocoelomic cavities are separated by a non-permeable membrane[(1)]. Fetoplacental unit is a source of large amounts of lysozyme[(2)].

Lysozyme intra-amniotic levels were found to increase according to the progression of gestation, reaching maximal values at term[(3)]. Exhibiting microbial growth-inhibitory activities lysozyme improves perinatal outcome[(4)]. However, lysozyme intra amniotic level patterns in high-risk pregnancies are not clearly understood.

Materials and Methods

Ammiotic fluid samples were obtained under ultrasound control in 82 pregnant women at the end of gestation. Forty eight specimens were from normal, while 34 were taken

from high risk pregnancies: Rh-alloimmunisation, hydramnios, diabetes mellitus complicated by pregnancy-induced hypertension, diabetes mellitus with Rh-alloimmumisation, and Rh-alloimmunisation complicated by pregnancy-induced hypertension. Signs of fetal distress were present in 18 cases. During the procedure, amniotic fluid specimen from the first Syringe was used for lysozyme determination and for the analyses the ACT was done for, in addition from the second one for microbial testing. Lysozyme activity was determined by original Behring kits (Testomar-Lysozyme Mono). Samples from the second syringe were inoculated onto blood agar and chocolate agar for aerobic microorgaisms and onto prereduced anaerobically sterilized peptone-yeast extract-glucose media, blood agar and chocolate agar for anaerobic microorganisms. Obtained specimens were also cultured for genital mycoplasmas by inoculation onto Mycotrim diphasic media (Hana Biologicals, Inc., Berkeley, Calif. USA) that was incubated 7 days. Microorganisms were identified with standard methods. Fluids contaminated with blood, those from patients complicated by ruptured membranes were discarded. Also, patients with clinical signs of premature labour were not included in the study.

Results

Investigating lysozme intra-amniotic levels we found significantly lower values in patients with Rh-alloimmunisation and those with diabetes mellitus and Rh alloimmunisation ($p<0.01$) (Table 1). In all these pregnancies there were signs of fetal distress.

Discussion

Antibacterial activity of amniotic fluid may protect patient from chorioamnionitis and resultant preterm delivery[4]. Lysozyme is confirmed to be the most important bacterial growth inhibitor. In the previous study

Table 1 *Intra-amniotic Lysozyme Level (Term Pregnancy)*

ACT indication	No. of patient	Lysozyme level (mg/l)		
		mean	SD	range
I-Term ACT	48	23.60	6.38	14- 28
II-Rh-alloimmunisation	15	7.20	4.83	3- 15
III-Hydramnios	7	22.14	7.62	14- 29
IV-Diabetes mellitus+PIH	6	17.50	1.64	16- 19
V-Diabetes mellitus+Rh-alloimmunisation	3	7.60	0.45	7.2- 7.8
VI-Rh-alloimmunisation+PIH	3	19.5	0.36	19.1-19.9

PIH-Pregnancy induced Hypertension

we confirmed that lysozyme levels increased according to the progression of gestation, reaching maximum at term[3]. Also, there was a strong relationship between high lysozyme level and sterile amniotic micro-environment [5]. In the present study all amniotic fluid specimens were sterile. A number of authors have previously described lysozyme concentrations in amniotic fluid[6,7]. But until now, only Porto et al[8] has reported that lyso-zyme concentrations were lower in high-risk pregnant women with signs of fetal distress. In this study we demonstrated that amniotic fluid lyso-zyme level exhibit a pattern of activity related to the pathological state of pregnancy. Namely, lysoyzme intra-amniotic levels were significantly lower in all patients with fetal distress, suffering Rh-alloimmunisation and those with diabetes mellitus and Rh-alloimmunisation.

In conclusion, lysozyme intra-amniotic levels could serve as a predictor of fetal distress.

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Reversal of Female Sterilization an Evaluation of 49 Cases at Maharaj Nakorn Chiang Mai Hospital

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Abstract : *Forty-nine patients underwent reversal of tubal sterilization between December 1981 and October 1991. The average age was 32.3 ± 3.6 years, mean parity was 2.2 ± 0.6 and mean duration from sterilization to reversal was 76.9 ± 42.3 months. Reasons for requesting reversal were a change in marital status, desire for more children and loss of a child. The most common site of anastomosis was isthmic-ampulla, followed by ampulla-ampulla.*

The mean duration of follow-up was 21.1 ± 20.2 months. During this period 37 pregnancies occurred in 30 patients giving a crude pregnancy rate of 61.2%. Ectopic pregnancy occurred in 13.5% and abortion in 24.4%. Twenty patients delivered at least one living child giving a take-home pregnancy rate of 40.8%. To account for incomplete and variable follow-up, life-table analysis was performed yielding cumulative pregnancy rates of 30.6%, 45.9% and 80.8% respectively at 12, 24 and 36 months after operation. Prognostic factors that may affect the pregnancy rate were studied in stepwise survival analysis with covariates (Cox Model). Only operative time, dextran use, location of anastomosis and age of the patients were found to significantly predict success after reversal. (Thai J Obstet Gynaecol 1994;6:23-32)

Key words : tubal sterilization, reversal, pregnancy, dextran

In the United States, it is estimated that about 10% of women who have undergone sterilization subsequently regret the procedure and about 3% will express interest in reversal. However, only 1% will be suitable for and undergo actual surgical reanastomosis, resulting in approximately 6500 surgical procedures per year[1]. Similar data for Thai women does not exist but our experience indicate that the demand for reversal of tubal sterilization is on the increase. Although microsurgical technique was

introduced into our clinic more than ten years ago, we do not, as yet, have data on its outcome. In this report, we present our experience regarding demographic characteristics of patients, reasons for requesting reversal, pregnancy rate and prognostic factors that affect the success of reversal procedures. Such information will be useful in patient counselling, in selecting proper patients for reversal and in optimizing the outcome of these procedures in the future.

Materials and Methods

In our clinic, couples requesting reversal of tubal sterilization will have detailed history recorded at their first visit. Female partners will be undergoing complete physical and pelvic examination. Preoperative evaluation includes semen analysis for male partners, complete blood count, routine urinalysis, chest film, serology for syphilis (VDRL) and diagnostic laparoscopy for females. In some cases, hysterosalpingogram is also performed to evaluate status of proximal tubes. Couples are counselled regarding the cost, the prognosis and possible immediate and late complications of the procedures including anesthetic risks, wound infection and risk of ectopic pregnancy. They are also strongly advised not to have surgery (but not rejected) if the male partners have oligoasthenospermia. Patients are not accepted for surgery if they have a remaining tubal length <4cm.

Ampicillin is given parenterally as prophylactic antibiotic in all patients. Surgery is performed with the aid of loupes 2.5x to 5x magnification, employing gentle tissue handling, fine bipolar coagulation for accurate hemostasis and constant irrigation with heparinized Lactated Ringer's solution (5000 units of heparin per 500 ml ± 5 mg dexamethasone). Under magnification, the occluded end of the proximal segment is identified and cut across using sharp scissors until clean and viable lumen is reached. The occluded end of the distal segment is then identified and a small opening that matches that of the proximal end is created by using fine forceps to hold a small segment of the tube and cut across with sharp scissors. After proper preparation of both the proximal and distal segments, tubal ends are brought together by placement of a 6-0 polyglactin (Vicryl) suture in the mesosalpinx right below the tubal serosa. Tubal reanastomosis is performed in 2 layers, using polyglactin (Vicryl) 8-0 suture. During closure of the first layer, the suture is placed in the muscularis at 6,3,9 and 12 o' clock respectively, avoiding the mucosa if possible. The serosal (second) layer is then approximated with interrupted sutures of 6-0 or 8-0 polyglactin. The patency is tested by injecting methylene blue (or indigocarmine) through the uterine fundus while occluding the lower uterine segment with Buxton clamp. At the completion of surgery, the pelvis is again washed with heparin-

ized lactated Ringer's solution and 6% dextran 70 in dextrose 250-500 ml instilled intraperitoneally. Since the value of dextran 70 in the prevention of postoperative adhesion is still controversial, its use is optional based on its availability in the hospital pharmacy and on the affordability of the patients.

In this study, infertile records, operative notes, in-and out-patient records of all 49 consecutive cases who underwent surgical reversal of tubal sterilization from December 22, 1981 to October 16, 1991 were reviewed. Additional information was obtained by sending a questionnaire to patients and by direct contact with surgeons who performed the operation. If the patients could not be reached by mail or if they did not respond to their second questionnaire, home visits were done to gather information from their neighbors, relatives and leaders of the villages. All data were keyed into dBase IV program and analyzed using BMDP programs on an IBM PC.

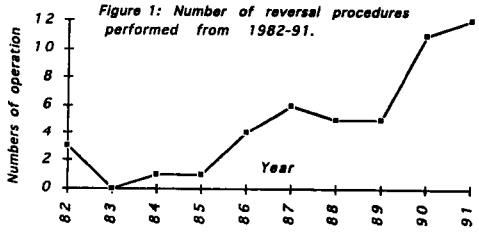

Fig. 1 Number of reversal procedures performed from 1982-91.

Table 1 *Residences of patients*

Province	Number	Percentage
Chiang Mai	32	65.3
- municipal	15	30.6
- suburbs	17	34.7
Chiang Rai	4	8.2
Lampang	3	6.1
Lumpoon	2	4.1
Nan	2	4.1
Maehongsorn	1	2.0
Payao	1	2.0
Pisanuloke	1	2.0
Prae	1	2.0
Rachaburi	1	2.0
Uttaradit	1	2.0
Tobal	49	

Table 2 *Occupation of patient*

Occupation	Number	Percentage
Merchant	12	24.5
Employee	10	20.4
Civil servant	10	20.4
Housewife	8	16.3
Agriculturer	7	14.3
Teacher	2	4.1

Results

The number of reversal operation increased from 1985 to 1991 (Fig. 1).

Most of the 49 patients in this study were residents of Chiang Mai and other nearby provinces (Table 1). The mean age of the patients (± standard deviation) was 32.3 ± 3.6 years, with a mean parity of 2.2 ± 0.6.

Most of them were merchants, employees or civil servants (Table 2).

Table 3 *Reason for requesting reversal*

Reason	Number	Percentage
Divorce and remarriage	27	55.1
Death of husband & remarriage	2	4.1
Desire for more children	11	22.4
Loss of a child	9	18.4

Table 4 Site of tubal anastomosis and pregnancies@

	Location of anastomosis					
	ampulla to ampulla (both)	cornual implant (both)	isthmus to ampulla & ampulla to ampulla	isthmus to ampulla (both)	Miscel-laneous #	Total
Not pregnant	4	1	1	10	3	19
IUP*	9	0	2	14	3	28
Ectopic	0	1	1	0	0	2
Total	13	2	4	24	6	49

@ Only the first pregnancy that occurred after reversal of tubal sterilization were included in this table

* IUP = Intrauterine pregnancy

Miscellaneous included: one case each of bilateral isthmus to isthmus anastomosis, isthmus to isthmus anastomosis on one side and isthmus to isthmus anastomosis plus fimbrioplasty on the other side, ampulla to ampulla anastomosis on one side and salpingo-oophorectomy on the other side, cornual implantation on one side and ampulla to ampulla anastomosis on the other side, and two cases where there were no record about the sites of anastomosis.

Pearson Chi square = 18.008, p = 0.0212, df = 8.

The mean time (±SD) from tubal sterilization to reversal was 76.9 ± 42.3 months, with a range of 6 to 192 months. Forty one of them (83.7%) had tubal ligation done in the immediate postpartum period and eight (16.3%) had interval sterilization (5 suprapubic tubal resection and 3 laparoscopic Falope ring procedure). The most common reason for requesting reversal was a change in marital status. Other reasons included desire for more chidren and loss of a child (Table 3).

The most common site of tubal anastomosis was isthmic to ampulla in 24 patients (49%), followed by ampulla to ampulla in 13 cases (26.5%) (Table 4).

The mean duration of operation was 188.3 ± 43.3 minutes. There was no immediate postoperative com-

Table 5 *Pregnancy rate after reversal among different surgeon**

Surgeon	A	B	C	D	E	F	Total
Not pregnant	10	3	3	2	0	1	19
Intrauterine pregnancy	16	6	4	1	1	0	28
Ectopic	2	0	0	0	0	0	2
Total	28	9	7	3	1	1	49

* Only the first pregnancy that occurred after reversal was included in this table
P = 0.8941 (Pearson Chi square test)

plication and the patients stayed in hospital for an average duration of 5.9 ± 1.3 days. The mean duration of follow-up from the date of operation to the end of the study on December 31, 1992, was 21.1 ± 20.2 months (range 1.6-133 months.) During this period, 37 pregnancies occurred in 30 patients, giving a crude pregnancy rate of 30/49 (61.2%). Intrauterine pregnancy occurred in 28 of the 49 patients (57.1%). Ectopic pregnancy occurred in 5(13.5%) and abortion occurred in 9 out of the 37 pregnancies (24.4%). First patient had two episodes of ectopic pregnancy without any subsequent intrauterine pregnancy. Second one had an ectopic pregnancy and was then lost to follow-up at 26.8 months after reversal. The other two patients had an ectopic pregnancy followed by one full term delivery. One patient delivered a stillborn baby at term and subsequently delivered a normal fullterm baby two years later. Overall, 20 patients out of 49, each delivered at least one living child, giving a take-home pregnancy rate of 40.8%.

Intrauterine pregnancy occurred in 56.1%, 60% and 66.7% of patients who previously had postpartum, suprapubic and Falope-ring tubal ligation respectively (p=0.478). Intrauterine pregnancy occurred in 26 of the 45 couples with normal semen anaysis and in 2 of the 3 couples whose male partners had oligospermia (defined as a sperm concentration of less than 20 x $10^{(6)}$. No pregnancy occurred in one couple due to asthenospermia (defined as forward motility of <50%). There was no statistical difference (p = 0.8941) in pregnancy rates among the cases operated on by anyone of the six surgeons in our clinic (Table 5).

Using Chi square test, there was also no statistically significant difference in pregnancy rates with regard to the use of dextran 70 (p = 0.2378) or the use of steroid in the irrigation (p=0.7563). However, there was a significant difference in intrauterine and ectopic pregnancy rates with regard to the site of tubal anastomosis (Table 4).

Nineteen patients were lost to

Table 6 *Life-table analysis of cumulative pregnancy rate*

Months after reversal sterilization	Number followed	Lost to follow-up	Pregnant	Exposed	Proportion Pregnant	Cumulative Preg. at end of interval
0 - 6	49	0	8	49	0.1633	0.1633
6 - 12	41	0	7	41	0.1707	0.3061
12 - 18	34	8	3	30	0.1000	0.3755
18 - 24	23	1	3	22.5	0.1333	0.4588
24 - 30	19	3	3	17.5	0.1714	0.5516
30 - 36	13	5	6	10.5	0.5714	0.8078
36 - 42	2	0	0	2	0.0000	0.8078
42 - 48	2	1	0	1.5	0.0000	0.8078
48 - 132	1	0	0	1	0.0000	0.8078
132 - 138	1	1	0	0.5	0.0000	0.8078

Table 7 *Summary of stepwise survival analysis with covariates (Cox Models)*

Step No.	Variable Extered	DF	Log Likelihood	Improvement Chi-square	p-value	Coefficient	SE	Exp (Coeff.)
0			-73.149					
1	Dur_Op	1	-69.956	6.387	0.011	-0.0274	0.0070	-
2	Dext_Use	2	-67.348	5.216	0.022	-1.7183	0.5963	0.1794
3	Location	3	-65.155	4.386	0.036	0.3425	0.1262	-
4	Age	4	-62.718	4.874	0.027	-0.1376	0.0623	-

Dur_OP = Duration of operation (in minutes)
Dext_Use = Dextran use (No or yes)
SE = Standard Error
Exp. (Coeff) = antilog of regression coefficient

follow-up at different time after the surgery. To account for such incomplete and variable follow-up, life-table analysis was performed, giving a cumulative pregnancy rates of 16.3%, 30.6%, 37.6%, 45.9%, 55.2% and 80.8% respectively at 6, 12, 18, 24, 30 and 36 or more months after surgery respectively (Table 6).

To evaluate for potential factors that significantly influenced the time to pregnancy after reversal procedures while statistically adjusting for other variables, the following factors were tested in a stepwise survival analysis with covariates (Cox Models) : age (years), method of tubal sterilization (postpartum, suprapubic or Falope-ring procedure), duration from tubal sterilization to reversal (months), surgeons (A,B,C,D and others), length of the longer remaining tube after reversal (centimeters), location of anastomosis (5 in all, as shown in Table 4), use of dextran (yes, no), use of steroid (yes, no), duration of

operation (minutes) and the presence of other pelvic pathology (yes, no). Four factors namely duration of operation, dextran use, location of tubal anastomosis and age of the patient at the time of the operation emerged as significant predictors (Table 7).

The analysis revealed that the chance for pregnancy decreased as the duration of the operation increased. In patients who were not givn dextran 70, the odds of pregnancy was only 0.1794 times of those who were given the medication. Bilateral ampulla to ampulla anastomosis was associated with the highest intrauterine pregnancy rate of 69.2% while no intrauterine pregnancy occurred in cases of bilateral cornual implantation. The age of the patient was found to adversely affect the time to pregnancy after reversal. In this regard, no pregnancy occurred in the two oldest women who were 39 and 41 years old at the time of their operation.

Discussion

Tubal sterilization is one of the popular form of contraception among new acceptors of contraceptive methods in our family planning clinic. Nowadays, there is a tendency to perform sterilization at a younger age. In this study, 40.8% of patients had been sterilized under the age of 30. When the age and the volume are taken into consideration, it is not surprising that there has been an increasing number of requests for reversal procedures. It is also noticeable that 84% of reversal patients had sterilization performed in the immediate postpartum period. These are times of special stress, and decisions made at such times may not be valid under less difficult circumstances. We recommend that more intensive counselling should be given to younger patients, with no more than two children, who request postpartum sterilization.

The most common reason for requesting reversal is divorce and remarriage, which is similar to those reported by Limpaphayom and Witoonpanich[2] and Yossing[3]. It is anticipated that the increasing divorce rate among Thai couples will result in an even higher increase in request for reversal in the future. The other contributory factor may be the fact that such services are now more readily available to patients at affordable cost.

In this study, the most common site for tubal anastomosis is isthmic-ampullary anastomosis which agrees with other reports of reversal procedures[3-7]. A crude intrauterine pregnancy rate of 57.1% in our series compares favorably with that of other reports from abroad i,e. 69% reported by Henderson[4], 75.4% by Owen[5], 64.4% by Seler[6], 60% by Winston[7], 64.4% by Gomel[8], 67.7% by Decherney et at[9], 57.5% by Grunert et al[10], and with reports from Thailand 69.2% by Limpaphayom and Witoonpanich[2] and 44.9% by Yossing[3]. Fifteen of the 28 intrauterine

pregnancies (53.6%) had already occurred within one year of reversal. This number increased to 20 (71.4%) within two years. It is, therefore, reasonable not to offer in vitro fertilization (IVF) to such couples before they have an adequate trial at conception for at least 1-2 years. Some authors[7,11] reported that isthmic-isthmic anastomosis has the highest success rate followed by isthmic-cornual and ampullary-ampullary anastomosis respectively. In this report, we have no case of isthmic-cornual anastomosis and only two cases of isthmic isthmic anastomosis, one of which was complicated by pelvic adhesion. This may explain why ampullary-ampullary anastomosis stands out as the most favorable site in terms of pregancy rate in our series. However, other authors such as Henderson[4], Seiler[6] and Grunert et al[10] were unable to identify a significant difference in success rate when comparing ampullary ampullary, ampullary isthmic and isthmic-isthmic anastomosis. Obviously, further study is needed in this regard.

Many authors considered tubal length as critical for success after reversal operation[8-9,11]. In this study, we required a minimum of 4 cm of remaining tube to be present before the patient was accepted for surgery. In this regard, we did not find that tubal length beyond the set minimum of 4 cm. had any prognostic implication on pregnancy rate. In multivariate analysis, we do find that the duration of operation, the age of the patient at operation, the use of dextran and the location of tubal anastomosis had prognostic implication on the success after reversal operation. The reason why operative time is important is not known. It is possible that the longer time used implies that anastomosis may not be proper and has to be revised, causing more tissue trauma and less chance of pregancy. Other possibilities such as less surgical skill and other associated pelvic pathology may also prolong operative time and decrease the success rate. Although there was no statistically significant difference in pregnancy rates among the six surgeons in this series, the numbers operated on by some of them are still too small to make a firm conclusion. The fact that no pregnancy occured in women 39 years or older at the time of operation suggests to us that the age limit of patients for reversal should be 38 years or less.

Several high-molecular-weight polymers have been evaluated as intraperitoneal solutions for adhesion prevention. Among others, the polysaccharride dextran of varying molecular weights and concentrations are presently of interest[12,13]. Utian et al[14] reported both a lower adhesion score and improved fertility when 6% dextran 70 or 32% dextran 70 (Hyskon) in dextrose was instilled intraperitoneally following bilateral tubal resection with subsequent anastomosis. Dextran appears to have a coating or siliconizing effect on denuded surfaces, preventing apposition

and adherence. Dextran also modifies fibrin structure, making it more susceptible to plasmin degradation.[12,13] Moreover, it creates an osmotic gradient producing ascites by drawing fluid into the peritoneal cavity. Such artificial ascites will produce hydroflotation effect and prevent tissue contact[11]. Studies in laboratory animal have almost uniformly shown dextran 70 to be effective in reducing adhesion formation after a peritoneal injury[15]. Unfortunately, clinical studies in human are conflicting. Two prospective randomized studies by the Adhesion Study Group[16] and Rosenberg and Board[17] showed dextran 70 to be quite effective in adhesion prevention, while another two randomized trials by Jansen[18] and Larsson et al[19] found dextran 70 ineffective in clinical usage. In our study, 6% dextran 70 was apparently effective in promoting pregnancy rate after reversal of tubal sterilization procedures. However, the study has limitation in that it was retrospective in nature and patients allocation to dextran use was not randomized.

Conclusion

Patients under 30 years of age with parity of 2 or less, who requested postpartum sterilization, should be carefully counseled before operation. Reversal sterilization should only be considered in women age 38 years or below. To optimize the pregnancy rate, we recommend the use of microsurgical techniques and dextran-70. If pregnancy does not occur within one or two years after reversal, in vitro fertilization should be offered.

Acknowledgement

The authors wish to thank Dr. Thawatchai Tansathitaya, Dr. Prayode Jongyusuk, Dr. Apichart Oranratnachai and Dr Pallop Pongsuthirak for their advice and helpful information on their patients. Thanks also go to staff and residents in the infertility clinic for their cooperation and encouragement.

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Home-made Knot-pusher for Extracorporeal Knot-tying

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Abstract : *The Clarke ligator (knot-pusher) has proved to be useful for laparoscopic suturing. Recent rediscovery of the instrument and its application has markedly simplified laparoscopic suturing and extracorporeal knot-tying. A home-made knot-pusher was made from solid stainless steel rod 4.5 mm in diameter, 350 mm in length. The opened circular tip was made with ordinary tools. All edges of the tip were smoothed and polished to avoid trauma to suture material and pelvic organs. The home-made knotpusher was tested with more than 100 knots on a pelvictrainer. The knots were secured without trauma to suture material. Thereafter, extracorporeal knot-tying was successful in 14 pelviscopic surgical procedures. We have found that the home-made knot-pusher can be easily made at a much lower cost and is convenient to use. Since high cost and length of operation time are the major disadvantages of laparoscopic surgery, a home-made laparoscopic instrument can lower the cost of surgery, without increasing operation time. Tip configuration should be further modified to make it even more suitable for laparoscopic surgery. (Thai J Obstet Gynaecol 1994;6:33-36.)*

Key words : knot-pusher, extracorporeal knot-tying, laparoscopic suturing, laparoscopic instrument, laparoscopic surgery

Many gynaecologic and general surgical laparoscopic procedures can now be performed with the help of new techniques and new instruments. One of the necessary techniques is laparoscopic suturing and ligating. In 1972, Clarke[1] described the Clarke ligator (knot-pusher) and a technique for suturing and extracorporeal knot-tying that proved to be useful for laparoscopic procedures. These instruments were developed in the Department of Obstetrics Gynaecology at the State University of New York in Buffalo. In 1974, Leventhal[2] recognized that these instruments could be the basis for a new era of laparoscopic surgery. Recent rediscovery with minor modifications, and their application by Reich[3] in 1992, has markedly simplified laparoscopic suturing and ligating. In a

developing country like Thailand, one of the many problems of laparoscopic surgery is the very high cost of imported disposable instruments. This report describes an easy way to make a knot-pusher at a much lower cost and demonstrates its use and application.

Materials and Methods

The home-made knot-pusher was made from a solid stainless steel rod 4.5 mm in diameter, 350 mm in length (Fig.1A). This stainless steel was supplied by a local metal store. First, the tip of the rod was flattened and rounded with a flat file (Fig.1B). The opened circular tip was made with a high-speed drill and hand saw (Fig.1C). All edges were smoothed with flat and round files and polished with muslin wheels, which were attached to a polishing motor (Fig.1D). After the final step, the tip was examined under X10 magnification, using magnifying glass. If any edges were not smooth the smoothing procedured were repeated. Extracorporeal knot-tying with the knot-pusher is easy. A simple loop is tied outside the peritoneal cavity and the knot pusher is applied to one strand (Fig. 2A). Holding both strands over the surgeon index finger, the knot is pushed through the trocar sleeve until it reaches the tissue to be ligated (Fig.2B). The second and third loops are then pushed down to secure the first, and the suture is divided with laparoscopic scissors (Fig.2C).

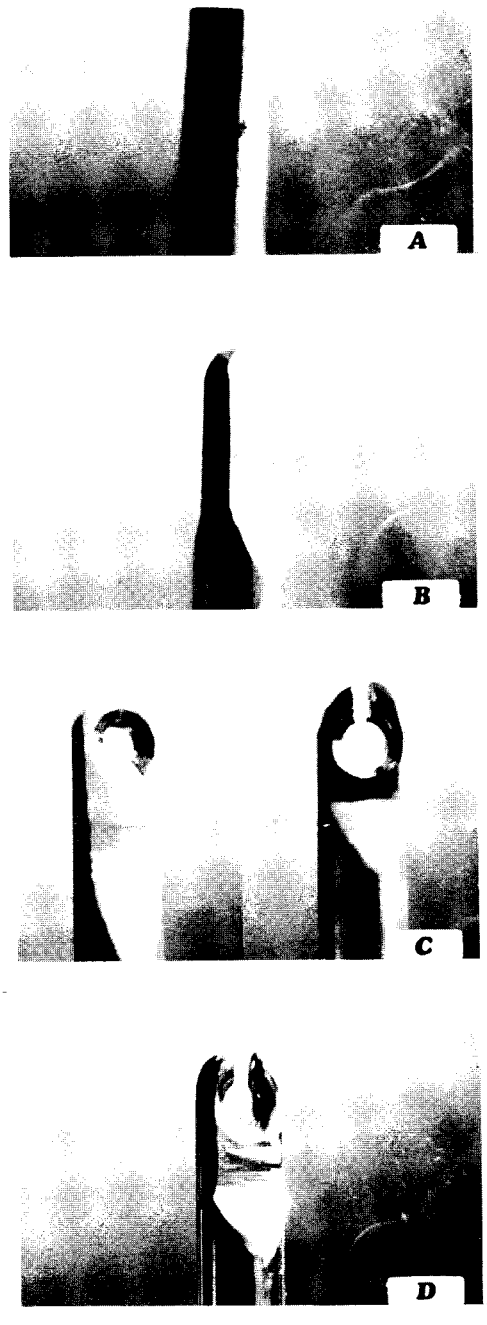

Fig. 1 Steps for making knot pusher.
A) Solid stainless steel rod 4.5 mm in diameter, 350 mm in length.
B) Tip is flattened and rounded.
C) The opened circular tip is made.
D) All edges are smoothened and polished.

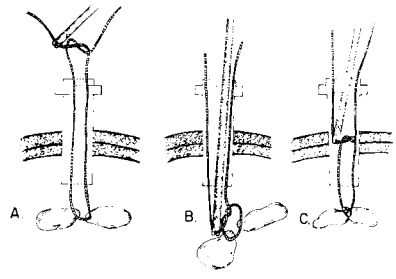

Fig. 2 Illustration of extracorporeal knot tying. A) Application of knot pusher to a simple loop. B) The knot is pushed through the trocar sleeve. C) The second and third loops are pushed down to secure the first.

Results

The home made knot-pusher was tested with a pelvictrainer. Various types of suture material were used, such as polydioxanone, polyglactin, polyglycolic or silk. It was tested with more than 100 knots without trauma to suture, and the knots were secured. Moreover, extracorporeal knot-tying was successful without complications in 14 procedures, as shown in Table 1. In this preliminary study, operative time, postoperative course and time in the hospital were similar to those of simple laparoscopic procedures. We have found that the home-made knot-pusher can be easily made at minimal cost and is convenient to use with the average time for each knot-tying less than 5 minutes. Moreover, its cost is only about 150 Baht (6US$) for a knot pusher. Instruments may be obtained by writing to the Department of Obstetrics and Gynecology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkla, 90112.

Table 1 Procedures using extracorporeal knot tying

Procedure	Number
Suture repair of ovaries	4
Ligation of IP* ligaments	6
Laparoscopic culdotomy closure	4

*IP = infundibulopelvic

Discussion

The Clarke laparoscopic ligator with opened circular tip, and its surgical applications, were described originally in 1972[1]. Other surgeons have devised similar instruments and methods for these procedures[2,3]. Ligation with the Roeder loop[4,5] is restricted to areas suitable for placement of the loop and limits variation of suture. The intra-abdominal forceps tie[6], using two forceps, directs effective forceps peripherally out of view of the scope, resulting in the greatest risk of slippage of suture and breakage. The modified half hitch knot[7] is tied extracorporeally and slid to the tissue, being approximated by pulling on the loose end. Here, there is considerable pull on the transfixed tissue since the knot dose not always slide readily. This is because it must overcome suture friction and the combined resistance of suture passage

through the tissue and of the knot through the abdominal wall incision.

Using the knot pusher, we can apply different suture material prepared extracorporeally directly to the tissue being approximated. Suture type can be varied by the surgeon as desired. The instrument is reusable. There is no pull on tissue being ligated. Suture moves only once through tissue in the dirction of the suturing needle. There is good visibility and tactile sensitivity. This instrument is increasingly being recognized as an important part of many laparoscopic surgical procedures. Ease of laparoscopic suturing and ligating greatly enhance the confidence of the surgeon, help decrease operation time, and contribute to increase the indications for advanced laparoscopic surgery. Since high cost and length of operation time are the major disadvantages of laparoscopic surgery, our home-made laparoscopic instrument can lower the cost of surgery without increasing operation time. Tip configuration should be further modified to make it even more suitable for laparoscopic surgery.

Acknowledgement

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Early Prenatal Diagnosis of Thanatophoric Dysplasia : A Report of Three Cases

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Abstract : *Three pregnant women prenatally diagnosed with thanatophoric dysplasia at 18, 19 and 21 weeks of gestation were reported. All of them were without significant previous medical and familial diseases. Sonographic evaluation was perfomed due to premature contraction or large for date measurements. In each of them, the sonographic findings demonstrated polyhydramnios, enlarged cranium, narrow thorax and severe micromelia of all extremities but normal ossification. Based on the sonographic features, the diagnoses of lethal short-limbed skeletal dysplasia were made and were most likely related with thanatophoric dysplasia however the pregnancies were terminated. Postnatal radiographs of all three cases showed the intact calvarium, normal ossification, large head size, narrow thorax with normal ossified ribs, flattened vertebral bodies (platyspondylisis, H-shape or U-shape), severe rhizomelic dwarfism but all the extremities wereextremely foreshortened, with femurs bowing. These findings were compatible with the diagnosis of thanatophoric dysplasia. (Thai J Obstet Gynaecol 1994;6:37-42)*

Key words : thanatophoric dysplasia, prenatal diagnosis

Thanatophoric dysplasia is a lethal skeletal dysplasia characterized by extreme rhizomelia, bowed long bones, normal trunk length but narrow thorax, and relatively large head. It probably represents the most common lethal skeletal dysplasia manifested prenatally. It occurs sporadically and is characterized by striking rhizomelic shortening, bowed limbs, polyhydramnios, narrow thorax and markedly flattened vertebral bodies.[1-3] The prevalence is approximately 1:10000 births respectively.[4]

Cases Report

Three pregnant women were seen at the antenatal clinic, Maharaj Nakorn Chiang Mai Hospital and were prenatally diagnosed withthanatophoric dysplasia at 18,19,22 weeks of gestation. Medical and obstetric histories

were unremarkable and no history of familial disease. The demographic data of these patients are summarized and shown in Table 1. The sonographic findings and postnatal appearance are summarized and shown in Table 2.

In each of them, the sonographic findings demonstrated hydramnios, enlarged cranium, especially case III, narrow thorax and severe micromelia of all extremities but normal ossification.

Based on the sonographic features, the diagnosis of lethal short-

Table 1 *Demograpic data of the pregnancies*

No.	Age	Parity	Weeks of diagnosis	Maternal complication	Indication for sonographic examination
I.	23	0010	18	Premature contraction	Premature contraction
II.	36	2002	19	Large for date Elderly gravida	Suspected of hydramnios
III.	26	0000	22	Large for date	Suspected of hydramnios

Table 2 *Sonographic finding and neonatal outcome*

No.	Sonographic finding	Mode of termination	Neonatal outcome
1.	- single fetus with breech presentation, - hydramnios - mild enlarged cranium with normal ossification (HC=18.2.cm) - severe shortening of all limbs but normal ossification - no fracture in utero - platyspondylosis	Spontaneous labour with oxytocin augmentation -	- female, stillbirth - bowed limbs and micromelia - narrow thorax - soft tissue redundancy - slightly enlarged cranium
2.	- single fetus in vertex presentation, - hydramnios - enlarged cranium with normal ossification (HC=20.4 cms) but no ventriculomegaly - severe shortening of all limbs but normal ossification - no fracture in utero	Condom balloon technique	- male, stillbirth, - mild generalized edema, - flat nasal ridge, - rather enlarged cranium with large fontanels, - bowed limbs and - severe micromelia - small thorax,
3.	- male fetus with hydramnios - large and globular cranium normal ossification (HC=28.3 cm) - narrow thorax with normal ossified ribs - normally ossified, flattened spine - severe micromelia and bowed limbs	Condom balloon technique	- male, hypotonia and died shortly after birth, - markedly enlarged, globular cranium with large fontanels - narrow thorax and short ribs - small scapulae - severe micromelia

HC= head circumference

Fig. 1 (Case I) The sonographic scan shows the shortened lower extremity. (TH =thigh, L=lower leg, F = foot, P=penis)

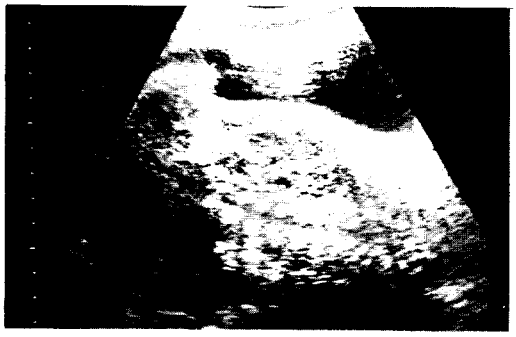

Fig. 2 (Case I) The longitudinal scan of spine shows the flattened vertebral bodies.

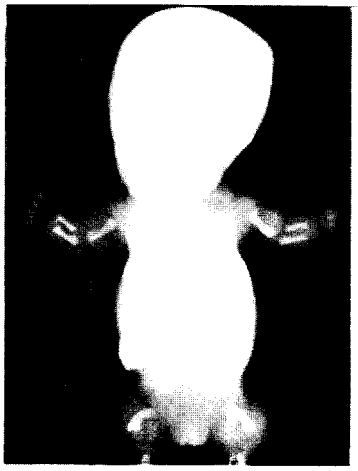

Fig. 3 (Case I) Postnatal radiograph confirms the prenatal findings. (mic-romelia with bowed femurs, enlarged head, and flattened vertebral bodies; H-shape)

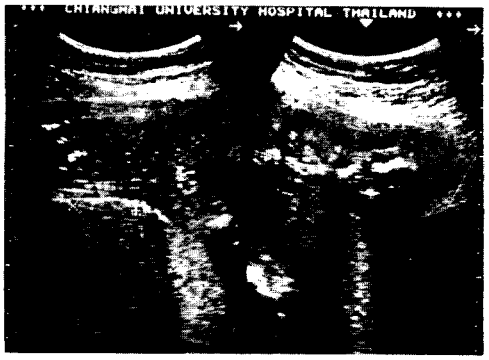

Fig. 4 (Case II) Left : The longitudinal sonographic scan shows narrow thorax x x, compared with abdomen + +, but normal ossification. Right : severe shortened long bones of upper extremities.

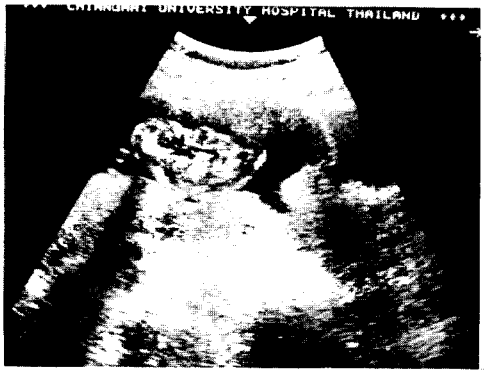

Fig. 5 (Case II) Sonographic features show the rhizomelia (extremely shortened femur)

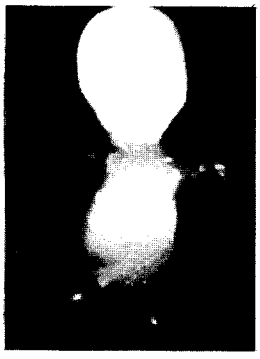

Fig. 6 (Case II) Postnatal radiograph confirms the prenatal findings. (mic-romelia extremely) shortened femurs, enlarged head, and flattened vertebral bodies; H-shape)

Fig. 7 (Case III) The scan shows markedly enlarged skull (right), compared with abdomen (left)

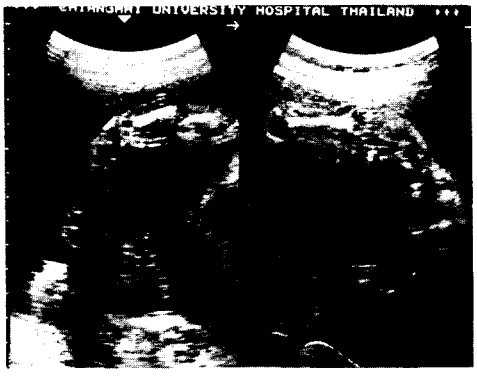

Fig. 8 (Case III) The scan shows severe shortening of long bones.

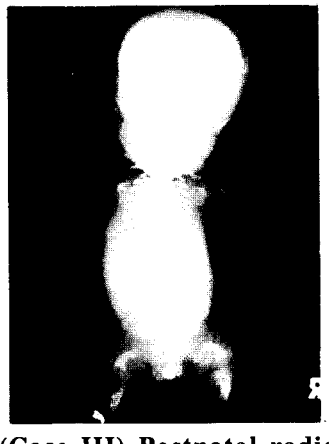

Fig. 9 (Case III) Postnatal radiograph confirms the prenatal findings. (micromelia markedly enlarged head, and flattened vertebral bodies; H and U-shape)

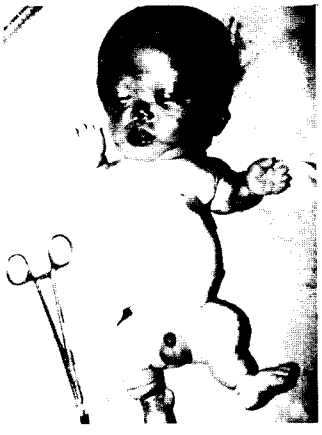

Fig. 10 Postnatal appearance of the fetus. (Case III)

limbed skeletal dysplasia were made and were most likely related with thanatophoric dysplasia and termination of pregnancies were carried out since the disease is uniformly lethal. Postnatal appearance and radiographs were consistent with prenatal sonographic findings.

Postnatal radiographs of all three cases showed the intact calvarium, normal ossification, large head size, narrow thorax with normal ossified ribs, flattened vertebral bodies (platyspondylisis), H-shape or U-shape, severe rhizomelic dwarfism, but all the extremities were extremely foreshortened, femurs bowing. These findings were compatible with the diagnoses of thanatophoric dysplasia.

The autopsy of each case confirmed the diagnosis.

Discussion

Thanatophoric dysplasia is a disorder of endochondral ossification

characterized by very abnormal histology of growth plate resulting in extreme rhizomelia, bowed long bones, normal trunk length but narrow thorax and relatively large head. With few exceptions, the reported cases have occured sporadically, in which case the sonologist will be the first to detect the unexpected deformity.[5] Because of the absence of familial risk, most cases were scanned for obstetrical reasons, usually large-for-date measurements during the third trimester of pregnancy. Approximately 50% of cases with thanatophoric dysplasia present with large-for-date measurements secondary to polyhydramnions,[5] including all of the cases reported here. The most useful finding that enables accurate prenatal diagnosis of thanathophoric dysplasia is the presence of the cloverleaf skull deformity. However, this deformity occurs only in approximately 14% of cases[6] and the cases reported here have no cloverleaf skull but relatively large head. In absence of cloverleaf skull, the disease should be reliably diagnosed when severe rhizomelic dwarfism, with rather large head, narrow thorax, platyspondyly and normal ossification are detected.

The presence øf cloverleaf skull is important since isolated thanatophoric dwarfism occurs sporadically, whereas the association of thanatophoric dysplasia and cloverleaf skull may be transmitted in an autosomal recessive manner[27] hence 25 percent recurrence risk. Therefore, the recurrence risk of the abnormality may not be negligible.

The prenatal differential diagnosis of short limbed dwarfism include 1) thanatophoric dysplasia, 2) osteogenesis imperfecta type II, 3) achondrogenesis, 4) severe hypophospatasia, 5) homozygous achondroplasia, 6) camptomelic dysplasia, 7) short rib polydactyly syndrome and 8) chondrodysplasia puntata (rhizomelic type).[8] The latter four entities produce characteristic features that most often permit distinction from the others. Of the former processes, with exception for thanatophoric dysplasia, they were charactrized by poor ossification. A specific diagnosis of thanatophoric dysplasia can be made on the basis of sonographic features alone, however, postnatal radiograph and histologic evaluation for definite diagnosis are required in many cases.

This report suppots that the lethal short-limbed skeletal dysplasia could be accurately diagnosed prenatally and pregnancy termination should be offerred whenever diagnosis is made.

Acknowledgement

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Midtrimester Amniocentesis for Antenatal Diagnosis of Genetic Disorder : Chulalongkorn Hospital Experience

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Abstract : *Results of amniocentesis for prenatal diagnosis at Chulalongkorn Hospital have been studied during June 1991 to May 1992. A total of 250 pregnant women with 261 amniocentesis fluid samples were included in this study. Most of the indications are maternal age older than 35 years. The incidence of chromosomal abnormality detection in the mother older than 35 years of age is 13.57/1000 amniocenteses, while no chromosomal abnormality detected in mother less than 35 years of age. We further analyse the two methods used for amniocentesis, one with ultrasound guidance and the other with ultrasound located at the site of puncture. The two methods did not differ in blood contamination in amniotic fluid nor the number of punctures. Also there was no abortion related to both procedures. The cost analysis for performing amniocentesis in the mother age beyond 35 is very reasonable according to our study. In conclusion, amniocentesis is a safe method for prenatal chromosome diagnosis and recommended for mothers who are older than 35 years old. (Thai J Obstet Gynaecol 1994;6:43-49.)*

Key words : amniocentesis, antenal diagnosis genetic disorder

Following the successful culturing of fetal cells from amniotic fluid by Steele and Breg[1] in 1966, midtrimester amniocentesis was established as a safe and accurate standard technique for prenatal diagnosis[2,3]. It has become a routine prophylactic examination, in developed countries, offered to women with an increased risk of having a child with a chromosome abnormality, neural tube defect or metabolic disease[4,5]. In Thailand, those who are at risk for having a chromosome abnormality fetus will be advised for midtrimester amniocentesis but not all of them have

been done due to the inavailability of genetic laboratory and inexperience of obstetricians. In Chulalongkorn Hospital, we have been performing amniocentesis since 1978 but few cases were done weekly at that time. Nowadays, with the development of high-resolution ultrasonography that makes the amniocentesis much safer, a program of midtrimester amniocentesis for antenatal diagnosis of genetic disorder has been set up with the aim of promoting obstetricians to refer the high risk group patients for amniocentesis.

The purpose of the present study is to assess the frequency of chromosome abnormalities in high risk pregnant women, the safety of the method and to evaluate the cost benefit for this program.

Materials and Methods

During June 1991 to May 1992, 250 women had chromosome analysis performed on 261 consecutive samples of amniotic fluid (6 pairs of twins). The indication of amniocentesis is shown in Table 1. Transabdominal amniocentesis was performed between 14-22 weeks gestation. When the date was uncertain, ultrasonography was performed earlier to confirm gestational age. During that period, amniocentesis was carried out by two methods : one by under ultrasonic guidance (UG) and the other by locating the largest pocket of amniotic fluid by ultrasound and then punctured by free hand technique (UL) : the first two authors. Since 1989, we have used linear real time ultrasound scanning (Hitachi, model EUB-40). In twin pregnancies, sampling from both fetal sacs were applied. To avoid maternal cell contamination, the first 2 mls. of amniotic fluid were aspirated and discarded in a separate syringe. Fetal chromosome analysis was carried out using trypsin -G - banding technique[6]. Using Chi's square to compare the statistical significant difference between outcome of the two methods used for amniocentesis and Chi's square with Yate correction where it is necessary.

Results

Of the 250 women performed amniocentesis at our hospital during the study period, 5 (1.95%) had to have repeat amniocentesis due to culture failure which might partly respond by bacterial contamination, transportation technique or culture

Table 1 *Indication*

Indication	
Elderly	212
IVF	11
Previous Chromosome abnormality	7
Family History of Chromosome abnormality	6
Habitual abortion	4
others	10
Total	250

Table 2 *Age Distribution by gestation*

Age \ Gestation	1	2	3	4	5	6	7	Total
20-24	1	3	-	2	-	-	-	6
25-29	1	-	4	-	-	-	-	5
30-34	8	5	3	2	-	-	-	18
35-39	52	63	32	21	6	3	-	177
>40	11	14	10	7	-	1	1	44
Total	73	85	49	32	6	4	1	250

Table 3 *Results of Amniocentesis*

Chromosome	N
46 xx	127
46 xy	126
47 xx + 21	1
47 xx + 21	1
47 xxy	1
Total	256*

* = 6 pairs of twins

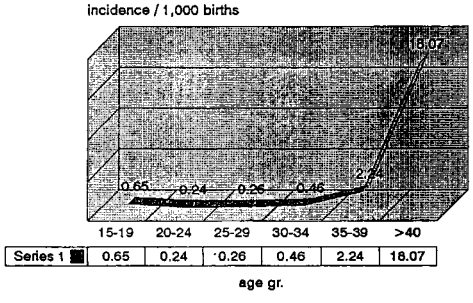

Figure 1 Incidence of chromosome abnormality and age of the mother who delivered at Chulalongkorn Hospital. (June 1991 - May 1992)

technique failure. Most of the indication (84.8%) (Shown in Table 1) was elderly gravida. The distribution of the women's age shown in Table 2, 221 (88.4%) were more than 35 years of age. Cytogenetic results and incidence of chromosomal abnormality are shown in Table 3 and 4, Figure 1. The number of amniocentesis using 2 different techiques are shown in Table 5. Some information was not available so only 243 punctures were included in this study. The results of both procedures are shown in Table 6 and 7. No abortion related to the procedure was found in our study.

Usually the cost of amniocentesis at Chulalongkorn Hospital is 2,500 - 3,000 bahts for a case. (These include the cost of ultrasound, amniocentesis procedure and cell culture, We have 221 mothers age beyond 35 who had amniocentesis during the study period. Three of them have

Table 4 *Resultsof Amniocentesis*

	No. of Mother *	No. of Amniocentesis	No. Revealing Chromosome Abnormality.	No. of Chromosome Abnormality	Incidence (1: 1000)
≤14	15	-	-	-	
15-19	1536	-	-	1[A]	0.65
20-24	4090	6	-	1[A]	0.24
25-29	3845	5	-	1[A]	0.26
30-34	2176	18	-	1[C]	0.46
35-39	894	177	1[A]	1[A]	2.24
≥40	166	44	2[A, B]	1[A]	18.07
Total	12,722	250	3	6	

* = Number of mothers who delivered at Chulalongkorn Hospital
A = Trisomy 21
B = 47 xxy
C = 45 xo

Table 5 *Method of Amniocentesis*

Ultrasonogram Guided	206
Ultrasonogram Located	37
Total	243

Table 6 *Number of puncture related to method of ammiocentesis*

No Puncture / Method Of Ammiocentesis	1	2	3	Total
Ultrasonogram Guided	200[A]	6	0	206
	(97.1)	(2.9)	(0)	(100)
Ultrasonogram Located	33[A]	3	1	37
	(89.2)	(8.1)	(2.7)	(100)
TOTAL	233	9	1	243
	(95.9)	(3.7)	(0.4)	(100)

A (P = 1.5091)

Table 7 *Amniotic Fluid (AF) colour related to amniocentesis through placenta*

AF COLOUR \ THROUGH PLACENTA	YES	NO	Total
CLEAR	91[A]	141[A]	232
BLOOD	7	4	11
TOTAL	98	145	243

A (P=0.040884)

abnormal chromosomes. The detection of one case of chromosome abnormality fetus will be simply calculated as followed :

Number of amniocentesis cases age beyond 35 years =221
Amniocentesis cost =3,000 Bhts
The total cost for amniocentesis =663,000 Bhts
Chromosome abnormality detected =3
Cost for one abnormality detected =221,000 Bhts

Discussion

The major cytogenetic indication for amniocentesis are advanced maternal age and chromosome abnormality in a previous child, conceptus, or family history of a chromosome abnormality child which contributes about 90% of all cases. Our study of cytogenetic results of 256 amniotic fluid specimens showed three abnormal karyotypes which were two trisomy 21 and one 47 XXY. Our rates for detection of chromosome abnormalities through amniocentesis according to single-year intervals of maternal age beyond 35 years were 13.57/1000. There was no chromosome abnormality detected from amniotic fluid specimen of women under age 35 years. However, six chromosomes abnormal offsprings were born after mothers of low risk or late antenatal care in the same period of our study at Chulalongkorn Hospital. Five of whom were trisomy 21 and the other was 45 XO. Of these, 4 chromosome abnormal infants were born after mother of less than 35 years of age. When considering the total number of chromosome abnormality fetuses and infants born after the mother who attended our antenatal clinic, we found that at age below 35 years, the prevalence of chromosome abnormality was 0.34/1000 pregnant women while at age 35 years up, the prevalence was 3.90/1000 pregnant women which was 10 times more than age below 35 years.

Since we have two techniques of amniocentesis : UG and UL, we further analyze the safety of each

method by comparing mainly the color of AF. The result shows that UG technique has a tendency to obtain less bloody amniotic fluid than UL technique, however, there is no statistical significant difference between these two techniques. Also, the number of percutaneous punctures between these two techniques have no statistical significant difference. These effects may be due to the small number of studied population and in part by the current experience of the authors who performed amniocentesis which need no accurate guiding. Nevertheless, UG technique seems to be the best method in performing amniocentesis if the facility is available. In our series there was no abortion or fetal death related to the procedure.

Regarding the value of amniocentesis, especially mothers whose age are beyond 35, the cost for one detected chromosome abnormality fetus is 221,000 bahts which is reasonable in performing a chromosomal abnormality detected program since the total cost for caring of the chromosome abnormality is much higher than the cost in the program.

Conclusion

Among a population of 250 pregnant women, a total of 256 amniotic fluid specimens were obtained for fetal chromosome analysis. Most of the indication was elderly gravida. Of the amniotic fluid specimens analyzed, 2 were Down's syndrome and 1 was 47 XXY. The cost of analysis revealed the benefit for performing amniocentesis in mother older than 35 years of age. The technique of ultrasound guided and ultrasound located amniocentesis seemed not to be different in the result of yielding the amniotic fluid. However, we accepted that the ultrasound guided technique is safe and practical for performing amniocentesis.

Acknowledgement

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Special Article

The Pathologist and Perinatal Medicine
Part I - Perinatal Epidemiology - Improving the Data Set

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Introduction

The perinatal pathologist can, as an integral part of the maternal-fetal medicine team, make a number of important contributions to this rapidly developing, stimulating and challenging field of clinical medicine. These include: -

1. At individual case level, providing diagnostic information to aid in planning the management of subsequent pregnancies at risk.
2. At hospital, regional and national level, improving the accuracy and validity of perinatal epidemiological data, and thereby contributing both to better surveillance of patterns of perinatal disease and to the overall planning of health care services.
3. At an individual case level, at unit level and on a regional basis, playing a key role in the quality assurance and auditing of new technologies, particularly those used in prenatal diagnosis, fetal therapy and neonatal intensive care.
4. Through liaison with colleagues in clinical pathology, encouraging the development of diagnostic laboratory services, technology essential, appropriate for supporting perinatal medicine and the effective use of expensive or scarce manpower and material resources.
5. By careful and thoughtful examination and evaluation of the individual fetus and placenta through collaborative and interdisciplinary studies contribute to the further understanding of developmental biology and of the pathogenesis and evolution of disease in the fetus and newborn.
6. In countries where there is an increasing tendency to litigation in obstetrics, provide an impartial opinion and act as an expert witness.
7. Provide an educational model to enhance the status of the autopsy as a central pillar of quality assurance and audit in clinical practice.

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Many of these functions revolve around the perinatal autopsy.[1] It is however obvious that full and detailed perinatal autopsy though highly desirable, may not always be possible or appropriate and that some of these objectives can be fulfilled without complete autopsy.

There are in addition several secondary roles for the pathologist in perinatal medicine. He or she should take responsibility for ensuring that even if no autopsy has been carried out, there is dignified and appropriate handling of the dead fetus or newborn in the hospital mortuary or histopathology department, that viewing of the baby is encouraged and that burial arrangements are not impeded in any way. Several techniques for rapid and cosmetically acceptable reconstruction of small fetal bodies after pathological examination are available and further contribute to improving the management of perinatal death. The pathologist may further contribute directly to the clinical management of perinatal bereavement by ensuring that fetal and neonatal mementoes such as pho tographs, footprints or locks of hair are collected and offered to the parents of the infant. The demand for this type of service varies among cultural, ethnic, religious and socioeconomic groups and is also influenced by the personal attitudes of the parents, the gestational age of the fetus, age and parity of the mother.[2] The perinatal pathologist may also become directly involved with counselling parents after a stillbirth or neonatal death[3]; again this is highly dependent on local resources and attitudes.

The Pathologist and Perinatal Epidemiology

The purpose of collecting any epidemiological data can be summarised as a process firstly of identifying a problem, then developing policy, strategy and options for action, implementing policy and finally evaluating outcomes. This is no less valid in perinatal epidemiology than in other areas of disease prevention. This paper, which is the first of two addressing the broader role of the pathologist in improving perinatal care and in advancing knowledge of the aetiology, pathogenesis and outcome of disease in the fetus and newborn, explores the contribution of the pathologist to improving the quality of perinatal epidemiological data. This aspect has been chosen in order to emphasise the value of quality epidemiological data for planning perinatal health services and for determining priorities for resource allocation, not only to tertiary level units but also at primary health care level to enable preventative strategies to be developed.[4] While the emphasis is on perinatal mortality data and its appropriate classification, other aspects of perinatal epidemiology will also be briefly discussed.

Regardless of whether data is intended to be used for planning health services or for comparison

between population, the validity and potential utility of perinatal statistical data, especially data related to mortality and to congenital malformations, is heavily dependent on the accuracy of recording of the original information and on the consistency of case definition .

There is a wide range of perinatal epidemiological data which the pathologist can influence positively or by omission and error render less valid (Table I).

Perinatal Mortality Data

Improving Quality and Utility

Perinatal mortality rate has long been used by clinicians, sociologists and politicians as an indicator of the quality and utilization of medical services in general, and for comparisons between various geographically, demographically and socio-economically defined population. While it has been lucidly argued that the perinatal mortality rate is no longer a useful or appropriate indicator of perinatal health[5], alternative indicators such as morbidity rates which may eventually prove to be more valid are much more difficult to define. As a crude indicator of overall level of medical care perinatal mortality rate is an easily definable parameter and has at least the advantage of being able to show changes over relatively short periods of time.

The reasons for collecting perinatal or any other mortality data are fairly obvious and include:

1. Monitoring longitudinal trends in overall rates.
2. Recording changes in the pattern and incidence of various causes of death.
3. Defining differences between disadvantaged and comparatively advantaged groups in a population.
4. Providing a basis for comparision between health care units and regions.
5. Providing a basis for confidential enquiries in a unit or region.

One of the original reasons for perinatal mortality surveys was to

Table 1 ***The Pathologist's Contribution to Perinatal Epidemiology***

Improving
. quality and utility of perinatal mortality data.
. quality and utility of maternal mortality data.
. ascertainment of chromosomal abnormalities and of congenital malformations.
. validity of twin studies.
. diagnosis and investigation of congenital and perinatal infections.
. surveillance of adverse outcome of high technology fetal and neonatal diagnosis and intervention.
. ascertainment of Sudden Infant Death Syndrome and other causes of sudden unexpected death in the neonatal period.
. information on outcome of randomised controlled clinical trials with high mortality.

allow confidential enquiry into individual perinatal deaths including assessment of avoidable and unavoidable factors. Now there has for sometimes[6], however, been a trend away from this approach to perinatal deaths. It is now much more common to evaluate patterns of perinatal death in such a way that attention is focused on specific areas of deficiency in perinatal care which seems to be more useful approach. Confidential enquiry is, however, still carried out on individual maternal deaths where the numbers are much smaller and preventable factors often much more clearly defined. Even though still generally accepted as a measure, however, crude of the effectiveness of health care, perinatal mortality rate alone is of limited value without cause specific information. Some process of classification is therefore required in order to identify specific issues and problems which permit specific recommendations for change.

Classification of Perinatal Mortality Data

Classification has been and continue to be a problem, in part because of the complex clinical situations which surround most perinatal deaths. It remains difficult to achieve agreement between obstetricians, neonatologists, pathologists and epidemiologists on the best classification system to use at hospital and local area level and even more difficult at national level. Any candidate classification system needs to be one which is designed to make use of data that is reasonably likely to be available or obtainable, and in such a form that subsequent data analysis can address those questions most likely to be asked by clinicians, regional health administrators, sociologists and politicians. Some of the requirements for a useful classification system are outlined in Table 2. It is only worth classifying perinatal mortality data if the results of the process lead to identification of deficiencies in perinatal care and of strategies for improvement. It is practical and logical therefore to approach perinatal death classification at several levels, depending on the available resources and the achievable outcomes.

The most obvious and primary distinction is between stillbirth (late fetal death) and neonatal death and

Table 2 *Design Criteria for a Classification System for Perinatal Death*

- Uses data that is easily available or obtainable.
- Uses a format that allows important perinatal issues to be addressed retrospectively.
- Has a small number of mutually exclusive categories.
- Is simple to use and able to be validated.
- Is not dependant on full and specialised autopsy.
- Allows second tier subclassifications to meet local needs.

difficulties in definition may arise even at this level. Nevertheless, the simple process of distinguishing between stillborn and liveborn infants at least enables two distinct groups of fundamental issues to be identified. Reduction in the stillbirth rate is, at least hypothetically, more likely to be achieved. 1. By primary strategies which target, by means of educational campaigns and antenatal screening programs, important maternal risk factors such as nutritional deficiencies, infections, chronic diseases, drug abuse and smoking, 2. By secondary strategies such as those aimed at improving access to antenatal care and thus enabling early detection and treatment of those maternal conditions that present defined risks to the fetus.

Reduction of the neonatal mortality rate depends not only on the availability of facilities and technology for neonatal intensive care but also, and perhaps more importantly in the developing world, on basic preventative health strategies to reduce the neonatal mortality from preventable causes such as birth asphyxia, infections, neonatal tetanus or hypothermia. Moreover, any strategy aimed at lowering the incidence of preterm birth such as those associated with eradicating those vaginal pathogens known to induce preterm labour[7] is also expected to lower the neonatal mortality and morbidity rate.

Reductions in the perinatal mortality rate in some categories of disease such as congenital malformations may, however, be misleading. Serum screening and ultrasound programmes to detect neural tube defects early in the second trimester, with subsequent termination of pregnancy, have resulted, not in a decrease in overall prevalence but merely in a shift in the numbers of deaths attributable to these malformations into the preregistrable age group where they no longer contribute to perinatal mortality figures.[8]

If strategies to reduce perinatal mortality are to be effective then classification by birth weight or birthweight/gestational age combination is also essential since, there is an inverse relationship between perinatal mortality rate and gestational age/birthweight.[9] It is, however, fairly obvious that simple separation into numbers of live births and numbers of stillbirths in each birthweight grouping will still not be sufficient to define problems in delivery of perinatal services.

Over the past 25 years, as perinatal epidemiology emerged as a subspecialty area it became clear that there was a need for cause-specific classification; numerous attempts were made with visible contributions from pathologists. Perinatal death classification by primary post mortem finding was first used in a large scale survey in Britain in 1958 and again in the early 1970s.[10] Retrospective assessment of these surveys clearly demonstrates the difficulties that arise in attempting to assign a primary cause of death particularly when there have been several interacting obstetric and neonatal factors as there are in a high

proportion of perinatal deaths. In a later modification([11]) of this essentially pathologically oriented approach it was pointed out that with the sophisticated imaging procedures and other diagnostic techniques available, a high degree of accuracy of pathological diagnosis was obtainable even without autopsy. The US Collaborative Perinatal Project[12] used a custom-designed classification based exclusively on placental and fetal pathological findings but had the intrinsic disadvantage of depending on full autopsy by specialist perinatal pathologists. Two studies from Finland[13,14] also rely on detailed pathological examination. None of these classifications are particularly helpful as some are cluttered with unhelpful and inappropriate diagnoses such as placental insufficiency or diagnoses such as cord knots which is the cause of death and requires more rigorous pathological evaluation than was usually appreciated at that time. For a long time, the most workable classification of perinatal death was undoubtedly the so-called Aberdeen classification[15] with its emphasis on primary obstetric factors leading to stillbirth and neonatal death. This classification remained for many years the cornerstone of much perinatal epidemiology. It can, however, become quite difficult to ascertain which one of a number of high risk obstetric factors, such as maternal glucose intolerance or pregnancy induced hypertension, which may coexist in a pregnancy, should be regarded as the primary obstetric factor leading to poor outcome. Nor is it always clear in any particular case whether the cause of death should be attributed to the underlying obstetric disease, for example, pregnancy induced hypertension, or to a superimposed acute obstetric event such as major abruption. The successor to the Aberdeen classification, devised by Whitfield[16] is now widely used as a substitute but suffers some of the same problems as its predecessor because of the need for hierarchical decision making.

It was in 1980 that a perinatal pathologist[17] devised what is now widely regarded as the best and simplest system, a two-tier classification based on birth-rate-specific groups and five mutually exclusive pathologically-based categories of disease. What is now universally referred to as the Wigglesworth classification was, as its designer has since pointed out[9] never intended as a classification but merely as a way of approaching the investigation of perinatal death. It is applicable to all perinatal deaths whether or not autopsy has been carried out. It is by far the most useful primary classification of perinatal death for individual hospital, local area or regional studies; it has not yet anywhere been rigorously tested at a national level. It is paradoxically the essential simplicity of the system that has been criticised by obstetricians and paediatricians in tertiary level centres who claim that it does not provide enough clinical detail to be

useful. This criticism can be easily addressed in these centres by the development, to suit local needs, of detailed subclassifications to enable identification of more specific obstetric or neonatal factors or, if obstetric factors only are required, the secondary use of a modified Aberdeen classification. The Wigglesworth system has been subject to one major validation study[18] and has, as a result, been slightly modified and it is this modification which will be used here to illustrate an effective way of classifying perinatal deaths. It is useful in areas where the autopsy rate is unavoidably low, either because there are too few pathologists to carry out perinatal autopsies or where cultural and religious attitudes discourage or forbid the practice, and yet where data of a type more specific than that derived from crude perinatal mortality rates alone is required to help with planning health care services. In addition to being widely accepted in Europe, it has been effectively used in a number of areas of the developing world[19,20] most notably in a major study in Jamaica[21] which remains a useful bench-mark for regional perinatal mortality surveys. It is of interest that this work[22] showed that during the period of the study when, for local reasons the autopsy rate was high, there were, in comparison to the period in which the rate was low, only minor changes in the percentage of deaths assigned to the various categories, most notably and predictably in the category of unexplained antepartum death and in category 5 (specific causes).

Clinicopathological Approach to Perinatal Mortality Classification

The Wigglesworth classification and its modification[18] have five mutually exclusive categories:

1. Antepartum fetal deaths - macerated stillborn infants in whom death is assumed to have occurred prior to the onset of labour unless there is clinical evidence to the contrary
2. Major malformations that would be likely to have resulted in death or multiple minor malformations, whether or not they suggest a specific syndrome.
3. Conditions associated with immaturity - liveborn infants weighing between 1500 and 2499 g and surviving the first day of life, and all liveborn infants weighing less than 1500 g provided groups 2 and 5 are not satisfied.
4. All fresh stillbirths, macerated stillbirths in which there was evidence that death occurred during labour, all liveborn infants weighing between 1500 and 2499 g dying on the first day of life, and all normally formed live-births of 2500 g and above provided group 5 is not satisfied.
5. Those infants with specific causes of death such as red cell isoimmunisation, fetomaternal haemorrhage or congenital infection.

These groups can form the

basis of a satisfactory primary level perinatal death categorisation and can be achieved even if no autopsy has been performed. If consent for autopsy is denied, or not sought, or if no pathologist is available then, a basic examination of the stillborn fetus or dead neonate can be carried out by obstetric or paediatric medical staff. Relevant investigations can be initiated on maternal blood, cord blood and placenta and classification categories then assigned. By using the simple sorting process outlined below, (Fig 1.) useful epidemiological data may be obtained even when there are insufficient human or financial resources to allow perinatal autopsy or where health care priorities dictate that resources be channelled elsewhere. Such an approach could, if carried out systematically in the delivery room, nursery, autopsy room, or pathology department, laboratory and the results recorded on a simple data sheet, suitable for future analysis, form the basis of an efficient and functional means of perinatal death classification with minimal effort. It should be recognised that without autopsies the proportion of cases in category 5 will be underrepresented.

Sorting Process for Investigation of Perinatal Death

The investigation of perinatal death may be seen as a stratified process of increasing levels of complexity depending both on local resources, on community, parental religious and cultural attitudes. Investigation at the first level can be carried out even if

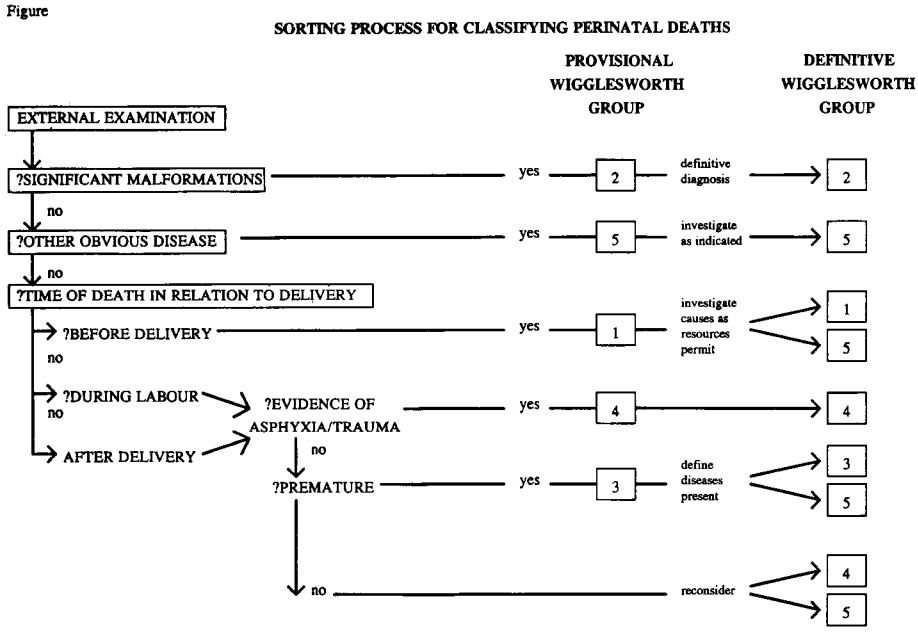

Figure 1. ***Sorting Process for Classifying Perinatal Death***

no pathologist is available since the basic examination can be carried out by the obstetrician or in the case of neonatal death by the neonatal paediatrician. The baby should be examined externally and any other accompanying diagnostic information such as ultrasound reports and neonatal x-rays reviewed to determine whether or not there are obvious malformations. Major malformations, whether single or multiple, place the baby in category 2. The findings of several minor malformations in a dead baby, even if these are not potentially lethal, should raise the possibility of a significant chromosomal abnormality and even if karyotyping cannot be carried out, also place the death provisionally in category 2. If significant malformations are absent then any other significant external abnormalities such as marked pallor, skin lesions such as petechiae or pustules, extensive haemorrhage or hydrops should be noted and accompanying clinical and laboratory data reviewed for evidence of specific disorders including red cell isoimmunisation and known or suspected congenital infections. If convincing evidence of a specific disease is found, then the death is provisionally classified into group 5. Suspected specific diseases can be further investigated using fetal, placental or maternal specimens; the extent of investigation depends on the resources available and the degree of detail demanded.

If there are no lethal congenital malformations or reason to suspect a chromosomal abnormality and no obvious signs of any specific disease then, for a stillborn fetus, the next stage is to decide whether, on the basis of its macroscopic appearance and using any clinical data available, the death occurred before the onset of labour or during labour. Determining whether signs of maceration are present is easy though attempting precise assessment of the period of time between intrauterine death and delivery is unwise. A normally formed fetus who convincingly shows no signs of maceration should be regarded as an intrapartum death unless there is cardiotocographic or other evidence to the contrary, and, unless there is also suspicion of a specific disease, should be classified into group 4 (asphyxial deaths in labour). The question of whether or not placental abruption is the underlying cause of an asphyxial type of death can usually be easily resolved and this provides an optional but important sub-category of asphyxial deaths (4b), to distinguish these cases from those in which asphyxia is related to the process of labour and delivery (4a). Known or suspected intrapartum deaths where no autopsy is to be carried out require careful external clinical and often radiological examination in order to identify clearly whether there is evidence of birth trauma. Cases with obvious major birth trauma are placed in group 4a along with birth asphyxia. Overwhel-ming fetal sepsis, such as that caused by group B Streptococcus,

and the acute fetal anaemia with hypovolaemic shock which may result from massive fetomaternal haemorrhage or a ruptured fetal vessel, may present an unexpected intrapartum death. These causes of death are relatively easily diagnosed with appropriate laboratory investigations but without necessarily needing an autopsy.

Group 1, the normally formed fetus dying before the onset of labour without obvious specific disease, is a large category which, depending on clinical and epidemiological resources available may then be sub-classified according to associated maternal, fetal and placental risk factors including pregnancy induced hypertension, maternal glucose intolerance and idiopathic intrauterine growth restriction. None of which are necessarily causes of death but factors predisposing to sudden death before labour. Truly unexplained antepartum death is a diagnosis of exclusion ideally requiring a very detailed autopsy protocol and extensive laboratory investigations analogous to that required for ascertaining the true incidence of Sudden Infant Death Syndrome and while highly desirable may be beyond the resources of many units.

Evaluation of neonatal deaths is again best approached by external examination of the baby and review of perinatal and postnatal records. If the baby is significantly premature and has lived for more than a few hours then autopsy is useful in order to evaluate the extent and severity of known prematurity related diseases such as hyaline membrane disease and its sequelae, pulmonary air leaks, periventricular haemorrhage, necrotizing enterocolitis and perinatally and postnatally acquired infection. It is particularly desirable that neonatal intensive care units, particularly those in the earlier stages of development, try to achieve a high autopsy rate in order to monitor the local incidence and pattern of iatrogenic disease and of complications of treatment. The term or near term baby born in apparently good condition, that who dies within the first few days of life also usually requires autopsy unless very obvious clinical factors have emerged. Specific conditions such as unsuspected congenital heart disease, overwhelming infection or metabolic disorders are not infrequently found, allowing classification of the death into category 5. If autopsy is not possible then it is again stressed that rigorous evaluation for preventable or treatable conditions such as birth trauma, severe anaemia and overwhelming infection is desirable.

The second level of investigation uses the same framework with some form of alternative, simplified or limited autopsy procedure. This can include radiographic examination[23], post-mortem ultrasound[24], limited dissection of for example chest, cranial cavity or abdomen, limited incisions through which most organs are examined or if the technology is available, ultrasound-guided or blind needle biopsy of organs. These proce-

dures may be useful when autopsy consent has been denied and resources are easily available for alternative investigations and when full autopsy is difficult because of a shortage of pathological expertise or enthusiasm.

The third level of investigation implies full autopsy examination by an experienced pathologist using standard techniques and with appropriately selected laboratory investigations; there is general agreement in the profession about quality standards at this level.[25-27] It should however be emphasised that an inadequately performed autopsy without appropriate tissue sampling and without understanding of the underlying clinical processes may be less helpful and more misleading than no autopsy at all. The general anatomical pathologist with no special knowledge is therefore strongly advised to consult an experienced perinatal pathologist and, in some circumstances, a paediatric radiologist, in any difficult case particularly where there is a suspected genetic basis to the disease, to avoid providing misleading information and thereby not only causing inaccurate prognostic information to be given to individual patients and subverting the clinical audit process but also contributing to distorting local epidemiological data.

When resources permit, especially, where there has been expensive and high technology fetal or neonatal diagnosis or intervention before death, a detailed autopsy is highly desirable. The value of the autopsy in this context will be the subject of a further paper.

Before leaving the subject of perinatal mortality classification the so called verbal autopsy should be briefly discussed. This is an epidemiological tool which has been widely used in some parts of the developing world, notably in rural Africa, to determine, by means of interviewing bereaved relatives, likely causes of death in adults and older children and has been recommended for use by the World Health Organisation as of use in assigning cause of death in trials of malaria control strategies. The uses and limitations of this method have recently been evaluated in a prospective study in Kenya.[28] It is difficult to see that such a method could ever have more than very limited use for providing cause specific perinatal mortality data except perhaps to identify very gross congenital anomalies and to crudely estimate the prevalence of deaths from certain conditions such as neonatal tetanus where the symptoms and signs may be well recognised by local population.

The usefulness of the Wigglesworth classification is that it highlights, at unit and regional level, deficiencies in perinatal services and thereby allows intervention strategies to be considered. A high incidence of deaths in group 1 may point to problems in access to or delivery of antenatal care. A high proportion in group 2 may indicate either a low uptake of antenatal screening for

malformations or, especially if occurring in a particular geographical area or occupational group, raise the possibility of environment teratogens. A high proportion of deaths in category 3 focuses attention on the adequacy of neonatal care, both primary health care, and availability of and access to neonatal intensive care services while in high proportion of cases in category 4 should direct attention to delivery room practices.

There remain major and well documented problems with the accuracy of perinatal mortality data, some of which are outside the sphere of influence of the pathologist. These include inconsistencies in defining and interpreting stillbirth versus early neonatal death, and failure to register deaths, particularly stillbirth and neonatal deaths of very low birth weight. In an elegant study in Belgium and the Netherlands, Kierse[29] highlighted the wide degree of personal variation in reporting deaths of very low birthweight babies; this variability can clearly have a major impact on the validity of perinatal mortality data. To this should be added the notorious inadequacy of the death certificate information often used for classifying causes of death when often inaccurate and based on poor quality information. All these problems apply in varying degrees to perinatal data collections at all levels ranging from national to local area to hospital-based data and can make both longitudinal and comparative studies difficult.

Maternal Mortality Data

In those countries where the maternal mortality rate remains very high, the solutions are clearly social and political not medical or as bluntly stated recently "educate or die".[30] It has, however, been noted[31] that in those developing countries where substantial advances have been made into reducing maternal mortality there is still a place for improvement in the quality of cause specific data and it is here that the pathologist can make an important contribution. In particular it is important that maternal deaths associated with abortions are not underreported, as is clearly the case in many countries.[32] The pathologist can try and ensure that if evidence of pregnancy or recent delivery is found at autopsy in any woman of reproductive age, it is clearly, unequivocally documented and moreover ensure that such deaths are reported to the appropriate hospital or local surveillance body. It is particularly important that any death in any woman in the reproductive age range, in particular any sudden and unexpected death, any death related to sepsis of unknown origin and any death from a medical condition known to be exacerbated by pregnancy be adequately investigated to ensure that a maternal death is not overlooked simply because it has taken place outside the context of clinical obstetrics. Although not always possible, it is highly desirable that autopsies be carried out on all maternal deaths and that these

Tble 3 *Improving ascertainment of congenital abnormalities*

- Recognising subtle markers of chromosomal syndromes in macerated and inexplicably growth retarded fetuses.
- Ensuring that karyotyping of malformed fetuses is carried out where indicated.
- Ensuring that descriptive reports and diagnoses are of adequate quality to permit accurate identification of congenital anomalies.

autopsies be performed by or under the direct supervision of a pathologist who not only has special interest and expertise in the subject but also has a sound understanding of clinical obstetrics. Unless unnatural causes of death are suspected, maternal deaths, regardless of, whether they fall under the jurisdiction of the coroner or medical examiner are better carried out not in the hectic atmosphere of a overcrowded forensic pathology service but in the more academic environment of a teaching hospital. These autopsies merit time and concentrated effort may yield much additional valuable information about the pathology of pregnancy.[33]

Data on Chromosomal Abnormalities and Congenital Malformations

There are, if resources permit and facilities for karyotyping are readily available, several ways in which the pathologist may improve ascertainment of chromosomal abnormalities and congenital anomalies in general. (Table 3)

The pathologist, or indeed any other person examining a dead baby, should remember the possibility of aneuploidy, particularly in macerated stillbirths who are small for gestation age and who have accompanying minor malformations. If this is recognised and if resources are available, then karyotyping can be carried out using fibroblasts cultured from placental tissue (particularly amnion) or pericardium. Significant chromosomal abnormalities are not infrequently found.[34] It is particularly important for the pathologist to be aware of this possibility in the macerated stillbirth as these babies rarely receive a formal clinical examination either from an obstetrician or neonatal paediatrician and therefore may be inappropriately classified as unexplained deaths.

It is, unless virtually unlimited resources are available, neither practical nor appropriate for either the pathologist or the obstetrician to demand, or even encourage, karyotyping of first trimester miscarriages or of morphologically normal second trimester fetuses. The general incidence of chromosomal abnormalities is well known from the large studies[35] and the recurrence risk of the same abnormality in future pregnancies usually low.

There is, however, a clear indication for karyotyping most obviously malformed fetuses, whether spontaneously aborted or electively aborted after prenatal diagnosis by

ultrasound, unless amniocentesis for karyotyping has already been performed, or the abnormality is an isolated neural tube defect. The finding of a major chromosomal abnormality associated with single or multiple malformation can make a major difference to the assessment of recurrence risk.

While the improved diagnosis of malformation sequences and syndromes has important consequences at the individual case level, it is equally important that the pathologist is consistently able to provide detailed descriptions of abnormalities and make intelligent overall diagnoses. This will lead to the collection of more accurate epidemiological data about the incidence and clustering of both chromosomal non chromosomal malformations lead to important questions, such as for example, those about occupational environmental teratogens, being addressed.

There is now considerable interest in the effects of paternal, as well as maternal exposure to potentially teratogenic chemicals before conception and various paternal occupations have been associated with adverse outcomes.[36] More extensive epidemiological studies are needed in this field and implicit here is the requirement for good quality pathogical data on fetuses aborted spontaneously or electively when there has been paternal exposure to putative teratogens. It hardly needs to be stressed, however, that proof of teratogenesis in human requires that a number of criteria be satisfied, including one that controlled epidemiological studies consistently demonstrate an increased incidence of a malformation spectrum in an exposed population[37,38]

Epidemiologists sometimes, however, use poor judgement when assessing malformations and classify birth defects in an inappropriate manner, for example, grouping limb reduction defects together with congenital amputations due to amniotic band sequence and leading to false conclusions about teratogens. Because of the recently emerging evidence linking limb reduction defects to chorionic villus sampling (CVS)[39], it is now recommended that all limb reduction defects in CVS exposed and non CVS exposed fetuses and babies are fully evaluated.[40]

Epidemiological studies on teratogenicity could be greatly improved if pathologists, alone or with medical geneticists and teratologists, had more input into the design, performance and analysis of these studies. Even if not formally involved in controlled studies, the expert pathologist can play a very critical role in evaluating the true incidence of certain important malformations and malformation sequences[41] and should be encouraged to do so.

The validity, usefulness and cost benefit of any regional or national birth defects or congenital malformation register is ultimately highly dependent on good quality ascertainment from all sources. It should be

remembered that one of the main goals of regional collections of data on birth defects must be to aid the investigation of avoidable factors causing birth defects and ultimately to enable collaborative research and development of prevention strategies as well as helping forecast medical and social services to accommodate changing patterns of non lethal abnormality.

Twin Studies

Scientific interest in twins and higher order multiple pregnancy has been focused on two areas in particular. One is the relative contributions of genetic and of environmental influences on development and disease, as revealed by twin studies; and the second, the specific pathology of multiple pregnancy, particularly the various abnormalities of monozygotic twinning. .It has been stated that the quality and usefulness of much of the material that has been written concerning multiple gestations is in direct proportion to the thoughtful precision and completeness of the pathological components of the descriptions and interpretations.[42]

There are several areas related to twin studies where the pathologist can play a role, though this is unfortunately not always fully appreciated by epidemiologists when twin studies are being designed or the data is being assessed. These include 1. verification of chorionicity of the placentas, 2. accurate assessment of malformations in twins, 3. documentation of the degree of concordance or discordance of these malformations, 4. verification of the sequelae of inter twin vascular communications, 5. improving the ascertainment of the different causes of excess perinatal mortality in twin pairs, and 6. clarifying the different patterns of disease at various gestational ages in like and unlike twin pairs. With the increasing availability of various forms of assisted reproduction and the subsequent increase in triplets and higher order multiple gestations, it is also important that comparable data is available in these types of pregnancies.

Placental examination is the most obvious contribution the pathologist can make to any twin study. Monochorionic placentas indicate monozygous twins and dizygosity can therefore be excluded if the placenta is pathologically confirmed as monochorionic. Twins of the same gender with single or fused dichorionic placentas may, however, be monozygous or dizygous. Most pathology associated with twinning occurs in those monozygotic twins who have monochorionic placentas with accompanying vascular connections and comprises a spectrum of abnormality ranging from inter twin vascular communication (twin-twin transfusion syndrome), so-called surviving twin syndrome with cerebral and other organ injury following intrauterine death of one of a pair of twins sharing a circulation, monoamniotic twins who have in addition a high risk of cord

entanglement and death, acardiac twin and the various bizarre patterns of symmetrical and asymmetrical conjoint twinning. In contrast, the problems of dizygous twins are usually obstetric in origin. Until prenatal ultrasound assessment of placental chorionicity becomes standard and the procedure has been sufficiently well evaluated in prospective blinded studies, routine pathological assessment of chorionicity will continue to be required.[43] In practice the only twin placentae that need to be examined pathologically (unless there are perinatal factors unrelated to twinning to be evaluated), are fused apparently single placentae of twins of the same sex.

Twin studies in general are based on the premise that by comparing a feature in monozygous and in dizygous twins, the relative contributions of genetic and environmental influences can be established.[44] In other words, studies of monozygous twins who are discordant for a given disease or malformation could, in theory provide a means of estimating the influence of early environmental factors while controlling for genetic factors. The existence of discordant malformations such as neural tube defects in monozygous twins is an obvious example and raises some interesting speculations about the differential influence of local intrauterine factors. There are, however, a number of limitations and inherent design problems in twin research and these have recently been critically discussed.[44] Furthermore, zygosity determination by blood grouping, chromosomal or DNA studies, may only be practical if reference laboratory facilities are available and the cost may be prohibitive. Placental examination may be inadequate or absent. Even in large and well designed twin studies[45], it is not always clear whether placental examination and pathogical evaluation of major fetal and neonatal abnormalities has been undertaken. The common general perinatal epidemiological problems of variable under reporting of fetal and neonatal death, and of definition of liveborn and stillborn also make comparisons of studies in different populations difficult.

Fetal and Perinatal infection

There is a small but important role for the pathologist in improving the quality of epidemiological information in this area. Underestimation of the true incidence of certain chronic and severe intrauterine infections such as congenital syphilis and congenital toxoplasmosis may occur unless a stillborn fetus or dead neonate is given a careful pathological examination. Maternal seroconversion does not necessarily mean that the fetus is infected; in the serious fetal infections such as toxoplasmosis, rubella, cytomegalovirus, varicella-zoster and human parvovirus, transplacental transmission occurs in less than one third of cases. Even if transplacental transmission occurs and the

fetus is infected, it is by no means necessarily affected and may be entirely free of the damaging tissue effects of the micro-organism at the time of birth. Even in areas of high prevalence it should not be uncritically assumed that perinatal death or specific pathology in a fetus of a mother who has seroconverted during pregnancy is a result of that disease.

Congenital syphilis can be easily missed in the macerated stillbirth or dead neonate unless one is familiar with the characteristic histopathological and radiological features of the disease which differ from those in the older infant.[46] Fetal infection with parvovirus B9 leading to hydrops and stillbirth has almost certainly been under reported in the past; pathologists are now very aware of the distinct and virtually pathognomonic viral inclusions seen in fetal tissue[47] and retrospective examination of archived tissue of hydropic fetuses using in situ hybridisation[48] has shown a considerable higher incidence of the disease than expected. In areas of high prevalence, congenital toxoplasmosis should be specifically considered at autopsy in all neonates and fetuses with a history of cerebral ventricular dilatation and periventricular echogenicity on ultrasound scan especially if signs develop rapidly.[49]

When a high prevalence of fetal disease is identified, then the cost benefit of antenatal screening in comparison with targeted educational programmes may need to be reviewed as is occurring with toxoplasmosis in France.[50]

Monitoring Outcomes of Invasive Fetal Diagnosis and Treatment

As the use of newer invasive forms of prenatal diagnosis such as chorionic villus sampling and fetal blood sampling become commonplace, it is important, both at hospital and regional level, to develop a process of formal surveillance to monitor outcomes and to identify and notify any patterns of abnormality which appear to be associated with that procedure, to enable subsequent evaluation. As well as notifying any malformations in liveborn infants subjected to invasive prenatal diagnosis, it is important that any fetus dying after an invasive prenatal diagnostic procedure be subjected to detailed pathological examination, not merely to assess obvious complications such as infection or haemorrhage but also to record any malformations, even if they are not the cause of death. As fetal therapy, including fetal surgery develop rapidly there is a good argument for formal registers, at national or international level. *Other issues related to audit of fetal diagnosis and therapy will be the subject of a further paper.*

Sudden Infant Death Syndrome in the Neonatal Period

Sudden unexpected death may occur between birth and 28 days of life. Accurate assessment of the true

incidence of Sudden Infant Death Syndrome in this period and its distinction from sudden death from identifiable causes such as overwhelming infection, unsuspected congenital heart disease, metabolic disorders and non accidental injury clearly depend, as it does in older age groups, on expert pathological examination, and usually falls into the area of expertise of the pathologist with an interest in perinatal and paediatric pathology, though in some jurisdictions the forensic pathologist may take responsibility. Since, in many countries, there are restrictions on access to this type of information and on communication between forensic pathologists and hospital pathologists, valid epidemiological data in this area of perinatal death may be difficult to obtain.

Clinical Trials with High Mortality

In randomised controlled clinical trials with an expected relatively high mortality rate, such as the ongoing United Kingdom multicentre trial of extra corporeal membrane oxygenation for acute but potentially reversible respiratory failure in the newborn, a comprehensive pathology protocol for examination of non-survivors is now regarded as essential. Should any form of fetal surgery such as repair of diaphragmatic hernia be proposed as the subject of a randomised controlled trial then a similar approach would be highly desirable.

Conclusion

Cause-specific epidemiological data can be used as a powerful tool for defining regional and national goals in health care and for guiding the development of new services and of prevention strategies in general[4] and in perinatal medicine in particular. The pathologist can play a central role in ensuring that this data is of highest achievable quality, both by encouraging autopsies where practical and where not by actively promoting the use of alternative means of investigating perinatal disease.

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