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In Vitro Fertilization of Human In vitro Matured Oocytes : Report of the First 22 Cases in Thailand

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Abstract : *This is the first report in Thailand, of the success of in vitro maturation (IVM) of human oocytes and in vitro fertilization (IVF) of those IVM-eggs. Preliminary results from a study period of 6 months showed that, from 22 patients, forty-nine immature oocytes were obtained via laparotomy or laparoscopy. About half (24/49) of those oocytes matured in vitro, two-thirds (16/24) of which were fertilizable. Among those fertilized eggs, nearly half (7/16) of them normally fertilized, and the remainders (9/16) ended up with polyspermic fertilization (>2 pronuclei). A number of normally cleaved embryos of 2- to 8-cell stage were transferred, while some of them were further cultured in vitro. Eventhough a few expanded blastocysts were obtained in vitro, none of the transferred embryos implanted successfully. Detailed materials and methods are described, and the results are compared to those of standard IVF. Physiology of normal and abnormal fertilization of IVM-oocytes are also discussed. (Thai J Obstet Gynaecol 1994; 6: 71-78.)*

Key words : in vitro maturation (IVM), in vitro fertilization (IVF)

Most IVF-programmes are now conducted with ovarian hyperstimulation protocols to achieve more oocytes than those of natural cycle. Routinely, these in vivo matured oocytes are fertilized in vitro and then cultured for a few days before transferring to the uterus. Due to high cost of ovarian stimulating hormones and negative effect of high level estradiol against implantation, superovulation regimen has been superseded by "natural" IVF in some centres[1]. With "natural" or unstimulation cycle, however, scrutinized monitoring of follicular growth and inconvenient timing of oocyte collection have become major drawbacks. A novel approach for this problem is to have the immature oocytes collected at any time of the

natural cycle and to have them matured in vitro (IVM-oocytes) before taking them into routine IVF-process. The obtainable embryos can then be transferred to the uterus at appropriate time or frozen stored for future use (Trounson AO, personal communication).

Based on the above information, the purpose of this report has been to study the growth and development of human IVM-oocytes before and after fertilization in vitro, and to study the feasibility of utilizing IVM-oocytes for routine IVF-programme in order to obviate the need for ovulation induction with its attendant costs, complications, and inconvenience.

Materials and Methods

This study has been carried out at this institution from January to June of 1993. A number of immature oocytes were aspirated from follicles, of less than 10 mm. in diameter, via either laparotomy (Phase-I) or laparoscopy (Phase-II). While the indications for laparotomy (n = 9) included a number of benign gynaecologic disorders such as uterine fibroids, endometriosis, or adenomyosis, all of those laparoscopy cases (n = 13) were infertile women who were scheduled for diagnostic laparoscopy. Informed consent was obtained from all of them after appropriate information was provided. All patients had spontaneous menstruations, and none was under any medication that could interfere with the ovarian cycle.

Phase-I was carried out to evaluate the plausibility of IVM-medium to support growth and development of IVM-oocytes. The IVM-medium was consisted of Tissue Culture Medium-199 (TCM-199) and 50% follicular fluid collected from preovulatory follicles of our standard IVF-cycles. This medium was then supplemented with 7.5 units of hCG/ml and 5.0 microgramme of estradiol/ml. Intraoperative aspiration of immature oocytes was performed by using a 20 gauge needle adapted to a syringe containing phosphate-buffered saline solution (PBS). The small follicles of less than 10 mm. in diameter were aspirated and washed a couple of times with PBS, and the contents observed under dissecting microscope. The immature oocyte-cumulus complexes (OCC) were then identified (Fig.1 & 2) and cultured in the IVM-medium. Twenty-four hours later, the OCC were evaluated for their maturation. Extrusion of first polar body confirmed their metaphase-II stage (Fig.3). Those oocytes that did not mature after 24 hours were cultured for an additional 24 hours under the same conditions as when the cultures were started. Following maturation in vitro, the oocytes were inseminated with fertile donor sperm which was prepared as previously described in our conventional IVF-protocol[2,3]. Eighteen hours later, fertilization was recorded and classified as normal (2-pronuclei: Fig.4) or abnormal (more than 2-pronuclei: Fig. 5). All of the

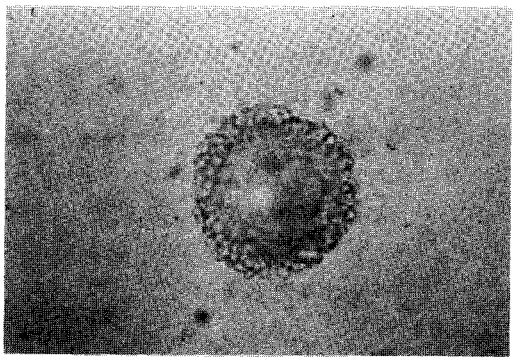

Fig. 1 Immature oocyte-corona-complex (OCC) showing a few layers of cumulus cells densely packed around immature oocyte (200x).

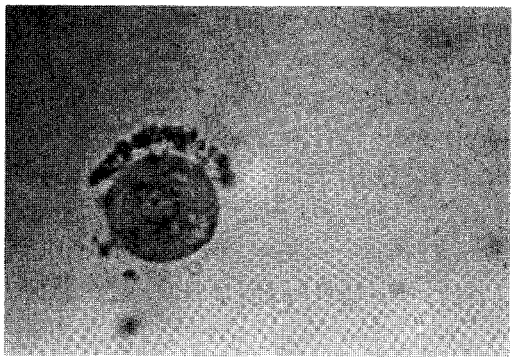

Fig. 2 Partially denuded immature OCC showing germinal vesicle with characteristically prominent nucleolus, centrally located in the cytoplasm (200x).

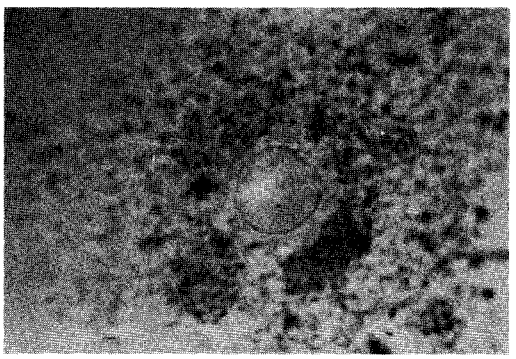

Fig. 3 In vitro matured OCC showing expanded cumulus mass surrounding metaphase II oocyte (extrusion of a polar body is noted) (200x).

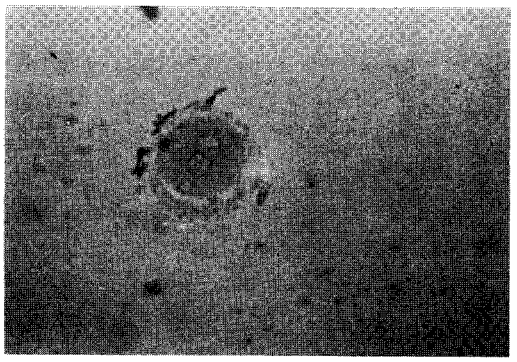

Fig. 4 Normally fertilized IVM-oocyte, 18 hours post-insemination (two adjoining pronuclei are noted) (200x).

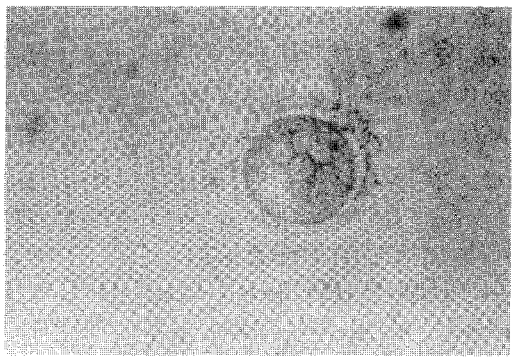

Fig. 5 Abnormally fertilized IVM-oocyte, 18 hours post-insemination (four adjoining pronuclei are noted) (200x).

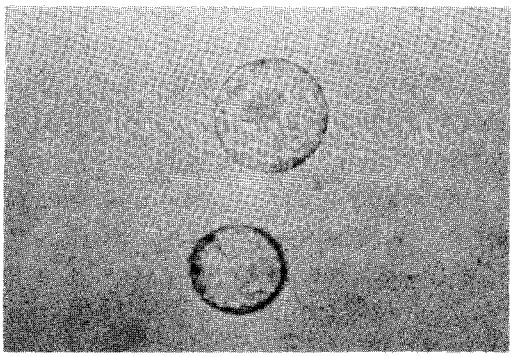

Fig. 6 Two fully expanded blastocysts, 5 days post-insemination (inner cell mass is clearly observed) (200x).

fertilized IVM-oocytes were further cultured and scored for their cleavage every 24 hours. No embryo transfer was attempted in Phase-I of this study.

Following the success of Phase-I study, Phase-II was carried out to determine the feasibilty of taking IVM-oocytes for use in routine IVF-programme. Via laparoscopy, the immature OCC were collected and processed as the above-mentioned procedures, except for the sperm used for insemination which belonged to each individual husband. Evaluational steps were also exactly the same as previously described, except that embryo transfer would be considered, in case "good-looking" cleaved embryo (s) was obtainable.

Statistical Analysis

For statistical comparison among groups, Chi-square test and Fisher's exact test were applied. A P-value <0.01 was considered as statistically significant.

Results

Table I shows comparable growth and developmental results between Phase-I and Phase-II IVM-oocytes. In Phase-I, about one-third of the immature oocytes matured in vitro and nearly two-thirds of those IVM-oocytes were fertilizable, even though a high proportion of abnormal fertilization (>2 pronuclei) were obtained. With further culture in vitro, nearly all of the fertilized IVM-oocytes cleaved normally, and a number of them had developed to blastocyst stage (Fig.6). In Phase-II of this study, the results showed the same trends as those of Phase-I. Among those 13 cases in Phase-II, three normally cleaved embryos were transferred, but none of them implanted successfully. In spite of abnormal fertilization, however, two cases of those fertilizable IVM-eggs subsequently got pregnant from their standard IVF-cycles (data not shown here).

Table 2 shows comparative results of standard or conventional IVF-cycles carried out at the same period as those IVM/IVF cycles. Significant differences were noted on maturation rates and per cent abnormal fertilization between these two groups.

Discussion

Preovulatory mammalian oocytes are maintained in meiotic arrest by an inhibitory follicular environment[4]. In response to the in vivo luteinizing hormone (LH) surge, a "positive signal" develops in the follicle. This positive signal overcomes follicular inhibition and stimulates maturation of the oocyte to the polar body one stage, which is receptive to fertilization[5]. When oocytes are removed from the inhibitory follicular influence and cultured in vitro, nearly all will spontaneously undergo incomplete maturation to the stage of germinal vesicle breakdown (GVBD)[6].

Table 1 *IVM/IVF results of Phase-I (laparotomy) and Phase-II (laparoscopy) retrieval of immature human oocytes from ovaries of natural cycles. No significant difference (P>0.05) was observed between any paired parameter.*

	Phase I (n=9)	Phase II (n=13)
Age (mean)	31-47 (38)	30-38 (34)
Cycle day	2-120	11-17
Number of immature oocytes	28	21
In vitro matured oocytes	10	14
Fertilized IVM-oocytes	6	10
2 pronuclear zygotes	4	3
>2 pronuclear zygotes	2	7
Cleaved embryos	5	10

Table 2 *Growth and developmental patterns of in vitro matured (IVM/IVF) versus in vivo matured (standard IVF) oocytes, before and after fertilization in vitro. * P=0.00004; ** P=0.000003 (Fisher's exact test)*

	IVM / IVF	Standard IVF
Number of cycles	22	71
Collected oocytes	49	577
Matured oocytes*	24/49 (50%)	443/577 (77%)
Fertilized oocytes	16/24 (67%)	342/443 (77%)
2 pronuclear zygotes**	7/16 (45%)	315/342 (92%)
>2 pronuclear zygotes**	9/16 (55%)	27/342 (8%)
Cleaved embryos	15/16 (94%)	326/342 (95%)
Embryo transfer cycles	2/22	64/71
Clinical pregnancy rates	0	13/64 (20%)

However, oocytes undergoing spontaneous maturation in vitro have much lower rates of polar body formation, fertilization, and pregnancy than those matured in vivo[7,8]. Cytoplasmic maturation, which is necessary for these events, has been found to be deficient in oocytes matured in vitro[9,10]. Therefore, it has been proposed that a positive signal be required to stimulate cytoplasmic maturation of oocytes cultured in

vitro[11]. These stimulatory factors have included gonadotrophins[12,13], steroid hormones[14], growth factors (EGF and/or IGF-I)[15,16], and other undefined substances in metaphase II egg cytoplasm[17].

For stimulated cycles, when immature human oocytes at the GV stage were recovered in clomiphene-HMG or HMG stimulated cycles and cultured in vitro, between 30% and 83% resumed meiosis, and after insemination, 33-82% of the metaphase II were fertilized. However, abnormal fertilization was raised (to 12%) and embryonic development seemed to be impaired as the incidence of pregnancy per transfer of IVM-oocytes was only approximately 12%, as compared to 25% for transfer of in vivo matured eggs[18]. Even with the granulosa cell coculture system, though augmented maturation and fertilization of immature oocytes have been accomplished, improved developmental competence could not be obtained[19].

However, a recent report has demonstrated that live births can occur in humans after in vitro maturation of oocytes. Cha et al[20] have shown that 56% of immature follicular oocytes recovered from unstimulated ovaries after ovariectomy and cultured in medium containing 50% follicular fluid, matured to metaphase-II stage. Of these, 81% fertilized, 64% cleaved normally and, in one patient with premature ovarian failure, the transfer of 5 embryos from IVM-oocytes resulted in the birth of triplets.

Very recently, Trounson et al[21] have developed methods of collecting immature oocytes (via laparoscopy and transvaginal ultrasound) from patients with polycystic ovaries and studied their maturation, fertilization and embryo development. The initiation of their first pregnancy was also reported via this novel technique. For the IVM-medium, they have been using a combination of FSH & LH (each of 0.075 unit/ml), estradiol (0.001 mg/ml) and hCG (0.5 unit/ml) in DMEM, incubated under 5% CO_2 at 37°C for 24-48 hours[22]. Of 95 germinal vesicle oocytes collected, 64% have been matured in vitro, and 25% of these have been successfully fertilized, a successful rate of about 15 percent per IVM-oocyte.

In this study, the original IVM-medium has been modified as such, in order to improve the developmental results of obtainable embryos (Oranratnachai A, unpublished data). Of 49 oocytes collected from 22 cases (Table 1), about 50% matured in vitro, two-thirds of which were fertilizable, and 94% of them cleaved normally. Therefore, a successful cleavage rate of around 30% per IVM-oocyte was obtained under this circumstance, making it comparable to those reported by Cha et al[20]. However, the number of oocytes in this preliminary study was too small for conclusion to be drawn, at this moment. Another on-progress study has been carried out to substantiate these encouraging results.

Compared to conventional IVF results, maturation rate (50%) of IVM-oocyte was significantly less than those in vivo matured eggs (77%). In spite of comparable fertilization rates, the proportion of abnormal zygote was obviously much higher in IVM-IVF group (55%) than that (8%) of standard IVF (Table 2). This clearly implied that (1) with this in vitro maturation system, developmental capacity of IVM-oocyte was rather limited; (2) nuclear maturation solely could not predict the fate of IVM-oocyte; (3) in addition to nuclear maturation, fully mature cytoplasm and membranes (zona & oolemma) are critically required for normal fertilization and embryonic development to be obtained (see[23] for detailed review). To solve these problems, extensive researches are urgently needed to produce the in vitro maturation system that is functionally equivalent to the in vivo one.

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Epidemiology of Maternal Mortality in Thailand

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Abstract : *A cross-sectional retrospective study of maternal mortality in Thailand was carried out for a period of 1 year, from 1 October 1989 to 30 September 1990 to evaluate the distribution, causes and characteristics of maternal deaths. Data were collected from hospitals, clinics, health centres of both government and private sectors. Maternal mortality rate was 27 per 100,000 live births, and highest in the Southern region. Age specific maternal mortality rate was highest in the aged group 35-39 years old. Most maternal deaths occurred in hospitals, doctors and nurses were involved because most of the severe cases were referred to hospitals. Low socio-economic status and education, lack of antenatal care, third trimester period and normal delivery were, factors commonly found among maternal deaths. Causes of deaths were haemorrhage, infection, preeclampsia and eclampsia and most of these were preventable. (Thai J Obstet Gynaecol 1994; 6: 79-90.)*

Key words : maternal mortality, Thailand, epidemiology

Maternal death is a major problem in maternal health among developing countries. No one knows exactly how many women died each year as a result of pregnancy. Approximately, half a million of women died, during childbirth and the majority of these deaths are preventable.[1,2] About 98 to 99% of these occurred in developing countries.[2,3] In Thailand, a decade ago, the maternal mortality rate is 40 per 100,000 livebirths.[4] However, detailed study in maternal death nationwide has not yet been carried out as well as in compiling with the World Health Organization Safe Motherhood Programme. This study was undertaken to find out the real situation of maternal death in Thailand.

Materials and Methods

1. Study design.

This study is a cross sectional descriptive study.

2. Data collection.

2.1 Place of data collection.

2.1.1 All Ministry of Public Health Service units including provincial hospitals, community hospitals, health centers,

mother and child hospitals and other health service units.

2.1.2 Private clinics and hospitals at provincial level participated in the Safe Motherhood project of the Ministry of Public Health.

2.1.3 University hospitals and hospitals in Bangkok were not included in this study.

2.2 Sources of data.

2.2.1 Medical records.

2.2.2 Death certificates.

2.2.3 Maternal death reports from Safe Motherhood project

2.2.4 Mother and Child Health Handbook.

2.2.5 Routine reports of provincial medical offices.

2.3 Methods of collecting data.

2.3.1 Questionnaires and manuals.

2.3.2 Informing the provincial medical officers on the study and questionniares.

2.3.3 Sending the questionnaires to provincial medical officers.

2.3.4 The provincial medical officers filed the questionnaire forms by using sources of data in 2.2. All variables in questionnaires can be found from the sources of data, particulary from maternal death reports.

2.3.5 Collecting the questionnaires.

3. Data Processing.

3.1 Checking the data by the staff of Family Health Division.

3.2 Coding the data by well-trained staffs.

3.3 Checking the coded data by the staff of Family Health Division.

4. Data analysis.

4.1 Analysis of data by using PC microcomputer 486 SX, the statistical package was SAS programme.

4.2 Statistic used were frequency distribution, percentage, mean, mode, standard deviation, specific rate and risk ration.

5. Variables in this study.

5.1 Number of live births

5.2 Number of maternal deaths

5.3 Place of delivery

5.4 Region

5.5 Age

5.6 Education

5.7 Occupation

5.8 Family income

5.9 Parity

5.10 Number of antenatal care

5.11 Gestational age at first visit

5.12 Gestational age at delivery

5.13 Type of delivery

5.14 Type of birth attendant

5.15 Causes of death.

6. Duration of study.

From 1st October 1989 to 30th

September 1990.

7. Financial support.

This study was supported by the Royal Thai Government under Mother and Child Health Programme and World Health Organization under THA MCH 001 Plan.

Results of the Study

1. Distribution of live births by region

There were 23.1 percent of live births in the Northern region, 33 percent in the Northeastern region, 32.8 percent in the Central region and only 11.1 percent in the Southern region. As a whole country, there were 794,370 live births during the period under study. The details of distribution of live births is shown in Table. 1

Table 1 *Distribution of Live Births by Region*

Region	Number of live births	Percent
Northern	183,334	23.1
Northeastern	262,518	33.0
Central	260,415	32.8
Southern	88,103	11.1
Total	794,370	100

2. Distribution of live births by age group of mother

Distribution of live births by age group of mother as well as number of women and age specific fertility rates are given in Table 2.

3. Distribution of maternal deaths by region

There were 211 cases of maternal deaths in this study. The maternal mortality rate of the whole country was 27 per 100,000 live births. The maternal mortality rate of the Northern region was 30 per 100,000 live-births and in the Northeastern region was 32 per 100,000 live births. In the Central and Southern regions, the maternal mortality rates were 11 and 50 per 100,000 live births respectively (Table 3).

Table 2 *Age specific Fertility Rates*

Age of mother (year)	Number of live births	Number of women	Fertility rate (per 1,000)
10 - 14	1,589	3,040,000	0.5
15 - 19	103,268	2,995,000	34.9
20 - 24	277,235	2,767,000	100.2
25 - 29	220,836	2,365,000	93.4
30 - 34	115,184	2,010,000	57.3
35 - 39	48,456	1,579,000	30.7
40 - 44	17,476	1,225,000	14.3
45 - 49	10,326	1,081,000	9.6

Table 3 *Distribution of Maternal Deaths by Region*

Region	Number of maternal deaths	Number of live births	Maternal mortality rate (per 100,000 live-births)
Northern	55	183,334	30
Northeastern	84	262,518	32
Central	28	260,415	11
Southern	44	88,103	50
Total	211	794,370	27

Table 4 *Age Specific Maternal Mortality Rate*

Age (years)	Number of maternal deaths	Number of live-births	Age-specific maternal mortality rate (per 100,000 live births)
below 20	25	104,857	23.8
20 - 24	49	277,235	17.7
25 - 29	43	220,836	19.5
30 - 34	43	115,184	37.3
35 - 39	33	48,456	68.1
over 40	18	27,802	64.7

Table 5. *Maternal Deaths by Place of Delivery*

Place of delivery	Number of maternal deaths	Percent
Regional hospital	33	15.6
Provincial hospital	72	34.1
Community hospital	51	24.2
Health centre	14	6.6
Home	38	18.0
Private hospital	3	1.4
Total	211	100

Table 6 *Education of Women in Relation to Maternal Deaths*

Educational Levels	Number of maternal deaths	Percent
Illiteracy (no education)	60	28.4
Primary school	76	36.0
Secondary school	39	18.5
High or Vocational school	25	11.9
University	2	0.9
Unknown	9	4.3
Total	211	100

4. Age specific maternal mortality rates

The age-specific maternal mortality rates are shown in Table 4. The maximum age of maternal death was 48 years old and the minimum age of maternal death was 13 years old. However, the mean age of maternal death was 28.5 years old with a standard deviation of 7.4 years.

5. Place of delivery

The maternal deaths occurred in regional hospital is 15.6%, provincial hospital 34.1%, community hospital 24.2% health centre 6.6%, home 18% and private hospital 1.4%. Details can be seen in Table 5. However, these statistics have to be interpreted with caution as denominators are not available for rates to be compared.

6. Education

From the study, it was obvious that most maternal deaths occurred in women with low or no education at all. There were 28.4% with no education and 36.0% primary school. There were 18.5% in secondary school level, 11.9% in high or vocational school level and only 0.9% in university education (Table 6). Again, these statistics should be treated only as crude indicators as denominators were not available for the computation of rates.

7. Occupation

With regard to this variable, maternal deaths occurred in housewives 47.4%, farmers 27.0%, employees 14.2%, government services 3.8%, business 3.3 and unknown occupation 4.3% (Table 7). These statistics should be treated as crude indicators as denominators for the computation of rates were not available.

8. Family income

Family income reflects the socio-economic status of women in relation to maternal deaths. In this study, family income was considered per month. As to be expected, most of the maternal deaths occurred among families in the lower income groups.

Table 7 ***Occupation of Women in Relation to Maternal Deaths***

Maternal Occupation	Number of maternal deaths	Percent
Housewives	100	47.4
Farmers	57	27.0
Employees	30	14.2
Government services	8	3.8
Business women	7	3.3
Unknown	9	4.3
Total	211	100

As denominators are not available these statistics should, again, be treated as crude indicators.

9. Parity

According to the parity, the maximum parity of maternal death was eleven and the minimum parity was primipara. Distribution of maternal death by parity and parity specific maternal mortality rate are shown in Table 9.

10. Number of antenatal care

There were many variation of antenatal care. The number of antenatal care varied from zero to nine times. No antenatal care accounted for all of maternal deaths. 26.1% had antenatal care between one to four and only 10.4% had more than 5 (Table 10).

11. Gestational age at first visit of maternal deaths

There were also variations of gestational age at first visit. They varied from 6 to 39 weeks of pregnancy among the dead mothers who attended the antenatal care. The gestational age of first visit is shown in Table 11.

Table 8 ***Family Income Per Month of Women in Relation to Maternal Deaths***

Family income per month (Baht)	Number of maternal deaths	Percent
Less than 1,000	13	6.2
1,000 - 1,999	82	38.9
2,000 - 2,999	75	35.5
3,000 - 3.999	30	14.2
4,000 - 4.999	5	2.4
5,000 - 5,999	4	1.9
More than 6.000	2	0.9
Total	211	100

Table 9 ***Parity Specific Maternal Mortality Rate***

Parity	Number of maternal deaths	Number of libe births	Parity-specific maternal mortality rate (per 100,000 live births)
1	132	370,177	35.7
2	29	239,899	12.1
3	21	100,091	21.0
4	8	41,307	19.4
5	9	19,859	45.3
Above 5	12	23,037	52.1

12. Gestational age at delivery of maternal deaths

There were 3.8% of dead motheres delivered in the first trimester, 9.5% were in second trimester and 86.7% were in third trimester. The maximum of gestational age at delivery was 42 weeks and the minimum was 10 weeks. Details can be seen in Table 12.

13. Types of delivery of maternal deaths

The types of delivery included normal delivery, Caesarean section, forceps extraction, vacuum and breech extractions. Details can be seen in Table 13. However, 14.2% were undelivered or aborted in this study.

Again, these statistics should be treated with caution. As to be expected, the highest frequency for ma-

Table 10 *Number of Antenatal Care Associated with Maternal Deaths*

Number of antenatal care	Number of maternal deaths	Percent
No antenatal care	134	63.5
1 - 4	55	26.1
More than 5	22	10.4
Total	211	100.0

Table 11 *Gestational Age at First Visit of Maternal Deaths*

Gestational age (weeks)	Number of maternal deaths	Percent
No antenatal care	134	63.5
1 - 12	12	5.7
13 - 28	56	26.5
29 - 40	9	4.3
Total	211	100.0

Tbale 12 *Gestational age at Delivery of Maternal Deaths*

Gastational age (weeks)	Number of maternal deaths	Percent
1 - 12	8	3.8
13 - 28	20	9.5
29 - 40	183	86.7
Total	211	100.0

ternal deaths were recorded in normal deliveries as most of the deliveries were expected to come under this category.

14. Types of birth attendant of maternal deaths

There were 4 types of birth attendants : doctor, nurse, midwife and traditional birth attendant. 52.6% of birth attendants were doctor. Nurse, midwife and traditional birth attendant were 22.7%, 6.6% and 18.0% respectively (Table 14).

15. Causes of maternal deaths

Most maternal deaths in this study were due to direct obstetric causes such as haemorrhage, infection, pre-eclampsia, eclampsia, ammiotic fluid embolism, septic abortion, rupture uterus, etc. Details are shown in Table 15.

Discussion

This study was a cross-sectional retrospective study for a period of one year from 1st October 1989 to 30th September 1990. The data of maternal deaths were collected from medical records and death certificates at hospitals, clinics, health centers and health service units of the country, both the Government and private sectors. These data were the most common sources used to estimate

Table 13 *Types of Delivery of Maternal Deaths*

Type of delivery	Number of maternal deaths	Percent
Normal delivery	114	54.0
Caesarean section	43	20.4
Forceps extraction	10	4.7
Vacuum extraction	9	4.3
Breech extraction	5	2.4
Undelivery or abortion	30	14.2
Total	211	100.0

Table 14 *Types of Birth Attendant of Maternal Deaths*

Type of birth attendants	Number of maternal deaths	Percent
Doctor	111	52.6
Nurse	48	22.7
Midwife	14	6.6
Traditional birth attendant	38	18.0
Total	211	100

Table 15 *Causes of Maternal Deaths*

Cause of death	Number of maternal deaths	Percent
Haemorrhage	86	40.8
Infection	24	11.4
Pre-eclampsia/eclampsia	21	10.0
Amniotic fluid embolism	18	8.5
Heart disease	14	6.6
Cerebral haemorrhage	10	4.7
Malaria	10	4.7
Septic abortion	9	4.3
Rupture uterus	7	3.3
Others	9	4.3
Unknown	3	1.4
Total	211	100

maternal mortality in developing countries[5]

During the study period, the maternal mortality rate of Thailand was 27 per 100,000 livebirths. The maternal death rate was highest in the Southern region, 50 per 100,000 livebirths, in contrast, the maternal death rate of Central region was lowest, only 11 per 100,000 live births. The maternal mortality rate among mothers in the Southern region was higher than that among mothers in the Central region with a risk ratio of 4.5. The maternal mortality rate in the Northern and Northeastern regions were also higher than that in the Central region with risk ratio of 2.7 and 2.9 respectively. The maternal death distribution was not homogeneous for the whole country. There were many considerable variations in maternal death. In the Central region, the health infrastructure, transportation, education and socioeconomic status were better than other regions. Most of the maternal deaths occured in the Southern region because it is remote and fundamentally very rural in some areas. Steep moutains and forests are obstacles to transportation and communication. Cultures and beliefs of people in this region as well as different religions upbringing are also the contraints. The accessibility of health services is also one of the problems. Some prefer to have child birth at home because of culture and beliefs and so the risks are increased when it is compared to others. Contraception, the strategy to prevent maternal deaths, is also neglected in the Southern region[6] The recent maternal mortality rate of Thailand was still high when compared to developed countries, for example, Europe, the United States of America and neighbouring countries such as Sing-

apore[7-15]. With regard to the characteristics of maternal deaths, it appeared that deaths occurred in mothers who were poor, uneducated, very young or very old, high parity and with no or inadequate antenatal care. These are high risk factors in pregnancy.[16] Improving standard of living, quality of life and education are the most important factors in the reduction of maternal deaths in Thailand. Increasing coverage of health services, adequate logistic, infrastructure as well as transportation and communication developmentd are also important strategies to solve maternal death problems.

The gestational age at first visit was also important. Early antenatal care was beneficial to mothers because they could obtain proper care and early detection of abnormality.[16] In this study, only 5.7% of mothers Commenced antenatal care in the first trimester, most come to the antenatal clinic in late pregnancy and some had no antenatal care at all.

Most of maternal deaths occurred in hospitals with doctors and nurses as birth attendants. The reason for this was that mothers who had severe complications were referred to the hospitals, often too late. Massive haemorrhage, convulsion and unconsciousness from eclampsia and sepsis had already occurred at home in these high risk mothers before they were referred to hospitals. As a result, the study showed that most maternal deaths occurred in hospitals and most of the birth attendants were doctors and nurses.

Causes of maternal deaths are also significant. The major causes of maternal deaths were haemorrhage, infection, pre-eclampsia and eclapmsia. These are direct obstetric causes which are preventable.[1,2] Similar to other developing countries, lack of budget, inadequate manpower and supply and ineffective management are the constraints in solving these problems.[1,2] Improving antenatal care, appropriate referral system, aseptic technique in delivery, adequate supply of blood, antibiotic and good transportation system are the most effective means of preventing and reducing the number of maternal deaths.

Conclusion and Recommendation of the Study

Conclusion

Like many developing countries, Thailand has a relatively high maternal mortality rate. During the period 1989-1990, it was 27 per 100,000 live births. The highest maternal mortality rate was found in the Southern region and the lowest in the Central region. The mean age of mothers was 28.5 with standard deviation of 7.4 years old. These mothers had little or no education and were from low socio-economic families. Inadequate or no antenatal care with delivery in the third trimester were common. The study revealed that doctors and nurses were the main

groups of birth attendants as most maternal deaths occurred in hospital. This was due to most of the severe cases were referred to hospitals often too late. Direct obstetric causes such as haemorrhage, infection, pre-eclampsia and eclampsia were most responsible for maternal deaths which could be prevented.

Recommendation

To reduce maternal mortality rate in Thailand, some recommendation may be proposed.

1. Increase coverage, quantity and quality of antenatal care.
2. Increase health education for pregnant women.
3. Conduct proper screening, identification and referral of high risk cases.
4. Monitor maternal health throughout pregnancy.
5. Supply adequate blood replacement.
6. Institute proper training for birth attendant.
7. Promote coverage and appropriate delivery care.
8. Promote coverage and appropriate postpartum care.
9. Encourage family planning.

The study show that the situation, with regard to authorities must implement policies and institute actions to lower the occurrence of death in mothers before, during or after child birth. The results of the study revealed that the problem is not purely a medical one, it is also socio-economic and education. To solve this problem, it needs community participation, appropriate technology and intersectoral collaboration. Primary health care should be an important tool to reduce maternal deaths.

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The Efficacy of Oral Clindamycin in the Treatment of Bacterial Vaginosis

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Abstract : *The efficacy of oral clindamycin in treating bacterial vaginosis was evaluated. In a descriptive study of 37 cases of reproductive-aged women with demonstrated clinical bacterial vaginosis on the presence of 3 out of 5 of the following signs (1) characteristically thin homogenous discharge ; (2) the vaginal pH > 4.5; (3) release of a fishy amine odor from vaginal fluid mixed with 10% KOH; (4) presence of clue cells (at least 20% of vaginal epithelial cells); (5) vaginal fluid contains few or no lactobacilli. The patients were treated with Clindamycin 600 mg per day orally for 7 days. Complete follow up was obtained one week after completion of medication. Of these 37 patients, complete response, defined as an absence of symptoms and presence of less than three clinical criteria, and partial response defined as an absence of symptoms but presence of three or more clinical criteria, were 94.5% and 5.5% respectively. Overall adverse drug reaction was 8.1% and all were mild and tolerable. Clindamycin is an alternative drug for the effective treatment of bacterial vaginosis. Its advantage over metronidazole is the absence of fetal teratogenesis during pregnancy. (Thai J Obstet Gynaecol 1994; 6: 91-99.)*

Key words : bacterial vaginosis, nonspecific vaginitis

Bacterial vaginosis (BV)is the most common cause of vaginitis among women of child-bearing age. The clinical entity is characterized by symptoms of increased amount of malodorous discharge. It is a conventional practice to diagnose BV only after excluding trichomoniase, vulvovaginal candidiasis and cervicitis, although these conditions may coexist. Amsel et al recommended clinical diagnosis basing on the presence of three or four of the following :[1] (1) characteristic homogenous white adhering discharge (2) elevation of the vaginal pH above 4.5 (3) release of a fishy amine odor from vaginal fluid mixed with 10% KOH (4) pres-

ence of clue cells (usually representing at least 20% of vaginal epithelial cell). These simple clinical tests are inexpensive and available in most gynaecologic office. Culture of the vaginal fluid usually reveals mixed microbial flora that typically include Gardnerella vaginalis, genital Mycoplasma and anaerobic bacteria such as Peptostretococcus, Bacteroides spp. and Mobiluncus spp.[2] Recent works have shown an increased risk of chorioamnionitis and prematurity among pregnant woman with BV, and suggests that BV may be a risk factor for pelvic inflammatory disease.[3-10] Many therapeutic agents have been used to treat bacterial vaginosis with various degree of success. There were many publications on oral metronidazole which showed that it was the preferential drug for the treatment of BV because it was more effective than other drugs previously used such as; ampicillin, tetracycline or topical sulfa cream.[11,12] However, metronidazole has the disadvantage of poor patient compliance due to high adverse drug reaction and potential fetal teratogenesis during pregnancy. Clindamycin, the other antibiotic which is particularly active against anaerobic bacteria, and moderately active against G. vaginalis and M. hominis, has been used as topical cream for the treatment of BV.[13] In the study, 2% clindamycin cream applied intravaginally once daily for 7 days showed an efficacy of 93%[13] In this study, oral clindamycin was chosen to confirm the efficacy against BV since it serves an alternative to metronidazole particularly for the treatment of recurrent BV and BV during pregnancy.

Materials and Methods

From January to May 1993, 37 females, aged 24-51 years old, attended the gynaecological out patient department clinic, Songklanagarind Hospital and were diagnosed as having bacterial vaginosis (BV). Those who were pregnant, lactating, prostitutes or having a history of antibiotic therapy during the last two weeks prior to the study were excluded. They were diagnosed as BV by the presence of at least 3 out of 5 criteria in the examination of the vaginal discharge; (1) pH above 4.5 (2) thin homogenous (3) fishy odor or amine test positive (4) clue cell at least 20% of total vaginal epithelial cells and (5) scanty or absence of lactobacilli.[14-15]

All cases went through a complete history taking and physical examination with particular emphasis on confirmation of urogenital symptoms and signs characteristic of vaginitis such as abnormal increased or malodorous vaginal discharge, vulvar irritation, pelvic discomfort and painful urination. The following procedures were performed for determination of BV and exclusion of other infections. The cervix was exposed with unlubricated speculum and Pap. smear was carried out by the standard VCE method. Vaginal discharge

adhering to the speculum was examined for the mentioned characteristics. The pH was determined by indicator Litmus paper (pH ranges 3.8-5.4). The amine test was performed by the addition of a single drop of 10 percent potassium hydroxide to a fresh drop of vaginal preparation. Positive result was considered if fishy amine like odor was liberated. Another drop of vaginal discharge was mixed with one drop of normal saline on a glass slide for wet mount preparation. The wet mount showed neither Trichomonas vaginalis nor Candida spp. Clue cells are vaginal epithelial cell which have their cell border obscured by bacteria during the observation in normal saline at 400 times magnification. A less objective feature is granular appearance of cytoplasm. Gram stain may also be used to identify these cells and usually shows a large number of gram variable coccobacilli with few or absence of gram positive rod lactobacilli.

The patients were diagnosed as having BV when examination of the vaginal discharge consisted of three or more criteria mentioned earlier. Recruited patients were given clindamycin 600 mg per day orally for seven days. Patients were advised to abstain from sexual intercourse until first follow up one week after complete treatment, in their nonmenstrual period.

Complete response was noted by the absence of symptoms and presence of less than three criteria in the examination of vaginal discharge whereas absence of symptoms with presence of three or more criteria were categorized as partial response. No response cases were those who had both symptoms and three or more of the criteria as mentioned above.

Results

Of the 37 recruited patients, all had complete dose of medication and there was no loss follow up. The mean age of patients entering the study was 34.86 years old. Most of them were government officials and house-wives. (Table 1)

Pre and post treatment symptoms were shown in Fig. 1. Abnormal increased amount of vaginal discharge, offensive odor were the prominent symptoms while pruritus was much less frequent. There were

Table 1 ***Demographic characteristic of studied patients***

Mean age	**34.6 years**
Occupation	
Government official	16 (43.2%)
House-wives	9 (24.3%)
Agriculture	2 (5.4%)
Trained worker	4 (10.8%)
Others	6 (16.2%)
Contraception	method
No contraception	10 (27%)
Condom	1 (2.7%)
Pill	2 (5.4%)
IUD	2 (5.4%)
DMPA	2 (5.4%)
Vasectomy	4 (10.8%)
Tubal sterilization	6 (43.2%)

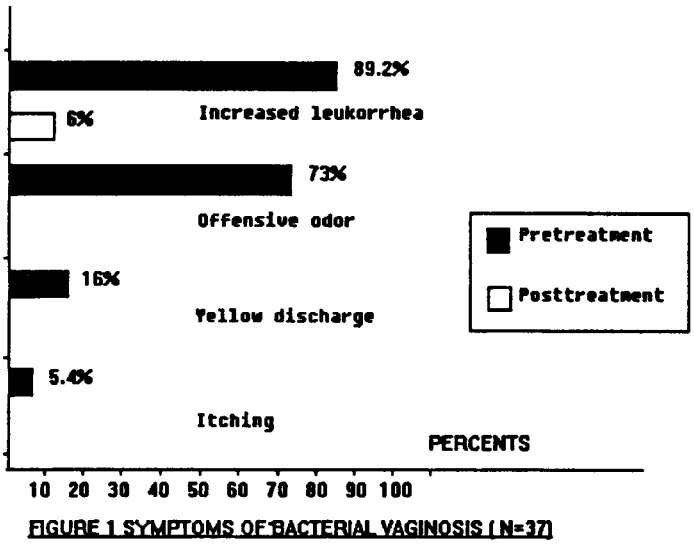

Fig. 1 compares the symptoms of bacterial vaginosis pre and post treatment.

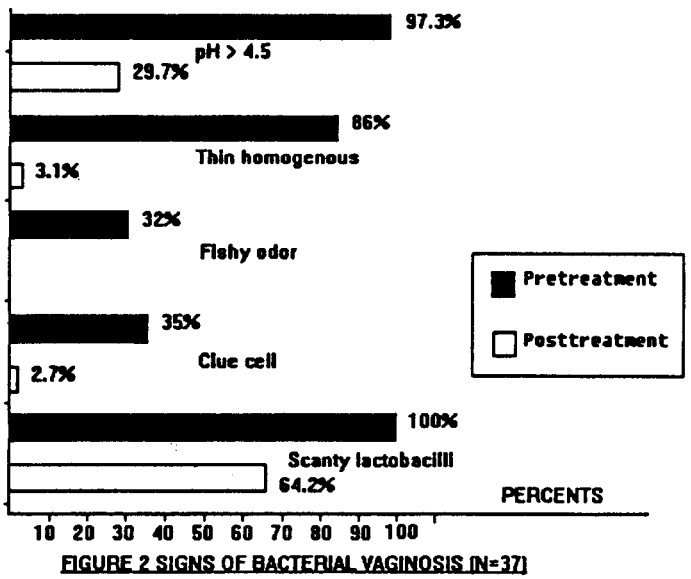

Fig. 2 compares the signs of bacterial vaginosis pre and post treatment.

no symptoms of dysuria or vaginal sores. After treatment, each symptom improved or disappeared. Changes in the characteristics of vaginal secretion before and after treatment are presented in Fig. 2.

With regard to the number of criteria during pre and post treatment (Table 2), it was noted that patients who had three or more criteria decreased from 100% to 5.4% after treatment. Complete response

Table 2 *Results of treatment, considering the number of criteria for diagnosis of bacterial vaginosis*

No. of criteria	Clindamycin treatment (N=37) Pre	Post
5	24 (64.9%)	0
4	13 (35.1%)	0
3	0	2 (5.4%)
3 or more	37 (100%)	2 (5.4%)
2	0	7 (18.9%)
1	0	18 (48.6%)
0	0	10 (27.1%)
Less than 3	0	35 (94.5%)

Table 3 *Results of treatment, considering response of treatment*

Response group	No. of patients (%)
Complete response	35 (94.5%)
Partial response	2 (5.5%)
No response	0

Table 4 *Adverse drug reactions of clindamycin.*

Nausea	1 (2.7%)
Vomiting	0
Dizziness	1 (2.7)
Others	2 (5.4%)

*One patient may have more than one adverse effect

94.5% complete response while partial response was 5.5%

Table 4 presents the adverse drug reactions of clindamycin found in 8.1% of the patients as follow nausea (5.4%), dizziness (5.4%), metallic taste (5.4%) and palpitation (5.4). All of them were minor and transient.

Discussion

Bacterial vaginosis resulted from the replacement of the normal vaginal flora with mixed flora consisting of Gardnerella vaginalis, anaerobics and Mycoplasma hominis. Since vaginal inflammation is not a feature of this infection the term "vaginosis" has replaced "vaginitis". We did not attempt to diagnosis BV based on bacterial isolation because it was not practical and might not be correct and also a variety of other bacteria in addition to G. vaginalis are important in this type of vaginal infection. Moreover, G. vaginalis can be recovered from up to 58% of those without clinical criteria for BV and can be found 6-63% in asymptomatic healthy women.[9,16-17] A positive culture in the absence of composite clinical signs of BV should not be used as a basis of therapy.[18] In this study, composite clinical criteria for

diagnosis of BV, recommended by Amsel and modified by Holmes were used in stead.[11]

Several regimen trials have shown that 5-nitroimidazole ánd its derivatives taken orally are effective for the treatment of BV. The two most common are 500 mg twice daily for 7 days and 2 grams as a single dose. The 7-day course has been associated with higher cure rates (79%-89%) in each of five studies in comparison with the single 2-gram dose (47%-85%).[18] The common adverse drug reactions include nausea, vomiting, anorexia, metallic taste in mouth, dizziness, and darkening of urine were reported to range from 2.6-26%.[19-22] Various skin rashes are less common, and the patients should not take metronidazole together with alcoholic beverages since the combination may produce disulfiram-like effects. Others reported the cure rate of 86% with less adverse drug reactions(8%) when a single dose of tinidazole was used.[23-24] Chandeying et al reported 3 different regimens of nimorazole with clinical efficacy ranged from 70% to 90%.[15] Although the efficacy of metronidazole is unquestioned, the toxicity of the drug has been brought into concern. Questions of mutagenicity and carcinogenicity remain unanswered. Use of metronidazole in pregnant women is generally not recommended[25] and the drug is contraindicated in first trimester of pregnancy and puerperium. Beta lactam antibiotics such as ampicillin, amoxicillin are effective against G. vaginalis however, resistant beta-lactamase-producing strains of one or more species of Prevotella or Porphyromona may be present in BV. Amoxicillin in combination with clavulonic acid have been used successfully but the beta-lactam agent has the disadvantage of destroying vaginal lactobacilli, already reduced in bacterial vaginosis, and may delay repopulation of the vagina with these organisms. These factors may be responsible for the low cure rate with the average of only 60% in the treatment of BV with ampicillin.[11,20,27-30] Hence, they do not appear to be effective for such treatment. Other antibiotics that are currently used include ciprofloxacin, cephalexin, tetracyclin and erythromycin. These drugs are less effective.[20,31] Erythromycin is less effective because macrolide antibiotics are not effective in acid pH of the vagina, therefore a study of the efficacy of oral clindamycin was done. The results of this study confirmed the clinical efficacy of clindamycin (600 mg. per day orally for 7 days) against BV. Treatment with clindamycin yielded complete response and partial response rate of 94.5% and 5.5% respectively. The efficacy was comparable to that reported by Lossick and Greaves.[32,33] It causes few side effects and well-tolerated by the patients. Clindamycin therapy could be particularly useful in the treatment of BV during pregnancy, in metronidazole treatment failure, and metronidazole intolerant cases. However, clindamycin is not

free from problems; it has been associated with pseudomembranous colitis.[34] The incidence of this side effect of clindamycin is unclear, but the reasonable estimate is about 0.01-1%.[35] None of the patients in our study developed colitis. Although we are not aware of any patients developing pseudomembranous colitis during the period of follow-up, we cannot be certain that this complication does not occur later, because we did not follow patients for more than two weeks after therapy. We believe that patients taking clindamycin should be informed about the possibility of bloody diarrhea and advised to discontinue the medication in such condition.

Summary

A descriptive study of the treatment of bacterial vaginosis was carried out in 37 reproductive-aged women. The patients were treated with clindamycin 600 mg per day orally for 7 days. Complete follow up was obtained one week after completion of medication. Of these 37 patients, the complete response, defined as absence of symptoms and presence of less than three clinical criteria, and partial response, defined as absence of symptoms but presence of three or more clinical criteria, were 94.5% and 5.5% respectively. Overall adverse drug reactions were 8.1% and all were minor as well as well-tolerated. Clindamycin is another effective drug for the treatment of bacterial vaginosis. Its advantage over metronidazole is in the absence of fetal teratogenesis in pregnant women.

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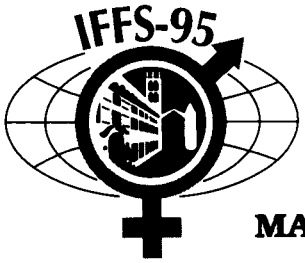

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Hysteroscopic Endometrial Resection : A Case Report

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Abstract : *Dysfunctional uterine bleeding is a gynaecological problem. In cases which are refractory to hormonal therapy, hysterectomy is often performed. However, there are instances when hysterectomy is contraindicated either medically or culturally or patients have no desire to undergo major surgery. For those women, endometrial resection offers an alternative treatment with less trauma, a short recovery phase and reduced uterine bleeding or even amenorrhoea. In this report a case of dysfunctional uterine bleeding was treated by hysteroscopic endometrial resection. Glycine 1.5 % was used as the distention medium and uterine pressure was controlled by Hysteromat (Storz). A valleylab Force 2 was used with a blend of 100 watts cutting current. The patient was discharged twenty four hours following the procedure. There was no complication and the result was satisfactory. (Thai J Obstet Gynaecol 1994; 6: 101-105.)*

Key Words : hysteroscopy, endometrial resection, resectoscope, dysfunctional uterine bleeding

The management of dysfunctional uterine bleeding that is satisfactory to both the patient and gynaecologist has always been a constant challenge. In cases which are refractory to hormonal therapy, hysterectomy is often performed. However, there are instances when hysterectomy is contraindicated or is undesirable to the patient. Currently hysteroscopy has an important role in these cases both as a diagnostic and therapeutic instrument. We reported a patient who failed to respond to hormonal treatment and did not want a hysterectomy. Endometrial resection was performed in such a case.

Case report :

A 38 years old, para 1, Thai woman presented with a history of abnormal uterine bleeding. In December 1986 she suffered from a ruptured endometriotic cyst of the right ovary. A laparotomy with right and left ovarian cystectomy were performed. Since 1987 she has also been a known case of breast cancer stage 2. Treatment was a modified

radical mastectomy and a complete course of tamoxifen therapy in July 1990.

The patient has complained of metromenorrhagia since June 1992. Curettage of the uterine cavity was performed in November 1992. The pathological report revealed secretory endometrium. She recieved a treatment with Provera (medroxyprogesterone acetate) for 7 months. However this medication failed to control the bleeding satisfactorily.

The patient was offered a hysteroscopic endometrial resection treatment and a counselling regarding the advantages and disadvantages of the operation including the operative procedure. Hysteroscopic endometrial resection was planned for March 22nd 1993. She received danazol 200 mg twice daily for two months preoperatively.

Technique of hysteroscopic endometrial resection

In the operating room the patient was placed in lithotomy position. General anesthesia, induced by Fentanyl, Droperidal and Dormicum, with Diprivan (total 600 mg) was administered in titrating dosage. One gram Rocephin was given intravenously at the start of the operation. The hysteroscope, with attached resectoscope, size 24 Fr with roller-ball (instead of cutting loop) was inserted into the uterine cavity after sounding and dilatation of the cervix up to Hegar No. 10. The hysteroscope was connected to a television monitor and video tape recorder. Glycine 1.5% was used as a distension medium. Intrauterine pressure was set at 100 mmHg. and the suction pump at 100 mmHg, controlling automatically by Hysteromat. The electrosurgical unit (Valleylab, Force 2) was set with a cutting current of 100 watts on blend 1, and a coagulating current of 50 watts.

The endometrial cavity was first inspected and the cornual openings were identified. Destruction of the cornu was performed with the use of the roller-ball, this was extended across the fundus to the opposite cornu (intra ostial orea). The roller-ball coagulation device was then changed to the backward cutting angle loop resector device and resection started at the 9 o'clock position, working anti-clockwisely around the cavity. The resected pieces of the endometrium were pushed up to the fundus. It is important to apply a steady pressure with a slow movement of the loop to ensure adequate removal of the endometrium and good hemostasis. The endometrium was resected down to the level just above the internal os. The pieces of endometrium were removed from the cavity with the use of the flushing curette. The resectoscope was re-inserted and the bleeding points were coagulated with the roller-ball. In this case, the duration of the procedure was 2 hours, glycine inflow was 7,200 ml, and the outflow was 6,000 ml. The patient was observed for 24

hours, serum electrolytes were checked two hours following the procedure and were found to be normal. Paracetamol was given to relieve abdominal discomfort. There was no complicaiton. The histological report on the specimen, in aggregate, showed thin and degenerated endometrium and superficial myometrium with adenomyosis.

Results

The patient was followed up at three month and six month intervals. During the first three months the patient had normal menstruation. During the last three months there was very little bleeding (2 pads/day) with a duration of 2 days and a 28 days cycle.

Discussion

For the past one hundred years in the development of hysteroscopy, progressive improvement in light sources, optical systems, distension devices, medium and elaborate electronic equipment have resulted in a wide variety of indications and benefits for its use in clinical gynaecology, including the management of dysfunctional uterine bleeding (DUB). According to a recent study by the New York State Department of Health, about 650,000 hysterectomies are performed in the United States anually. Of these numbers approximately 8-10% are due to abnormal uterine bleeding.[1]

Currently abnormal uterine bleeding constitutes the most common indication for conventional hysterectomy, accounting for 22.1-81% of all hysterectomies. The resectoscope is probably the most useful of the last generation of hystero-surgical instruments. It permits major uterine surgery and is rendering obsolete many hysterectomies.[2]

Nowaday endometrial resection is more effective than curettage, less traumatic than hysterectomy and more rapid. It is less expensive and carrying a lower morbidity than that of laser ablation. Curettage remove only part of the functioning endometrium, but endometrial resection can destroy both the endometrium and the first few millimeters of the myometrium, thereby inhibiting endometrial reformation.

Endometrial resection is recommended for women who are multiparous, who have no desire for further pregnancy and have failed to respond to medical therapy. Pre-operative investigations should be done to fully evaluate hormonal and haematological status.

Pre-operatively the patients should be treated with hormones, either GnRH agonist or danazol for at least 4-6 weeks prior to the operation.[3] This is to render the endometrium less vascular and therefore reduce the amount of tissue debris and bleeding that would obscure the view during the procedure. In this case the patient was treated pre operatively with danazol 200 mg twice daily for eight

weeks, as the timing for the operation was postpone according to the patient desire.

The resectoscope, in this case, used high frequency current at a power of 100 watts blended 1 and 50 watts coagulation for endometrial resection. This resulted in effective haemostasis without carbonization, therefore rendering the procedure relatively bloodless.

It is unlikely that all of the endometrium can be resected, especially at the cornual region. Magos had used a forward angled loop for cornual and intra-ostial resection. In this case the roller ball was used instead of the forward angled loop as it was not available. For complete amenorrhoea, the resection should be taken to the upper half of the endo-cervical canal.[4]

Complications from endometrial resection are infrequent. These can include uterine perforation, haemorrhage, dilutional hyponatraemia, infection and subsequent pregnancy. Injury to the adjacent bowel has occured in a few patients. post-operative haematometra may occur after weeks, months or even years.[5]

The risk of perforation and haemorhage is likely to occur if the resection is not performed as a step by step procedure with a uniform depth of resection of the myometrium of 2-3 mm. as the optimum. The most likely area for perforation is the cornu as it is relatively thin. It is also important to maintain the correct scopecamera orientation.

Intravasation of the distention fluid medium is one of the major risks ; therefore, to minimize this, the depth of the myometrium resected should not be more than 5-6 mm. Also a prolonged surgical procedure can lead to intravasation of the medium resulting in fluid overload. In this case Glycine 1.5% was used as the distension medium. The amount of outflow fluid was less than the inflow by approximately 1,200 ml. This included leakage and absorption. It is important to record the amount of inflow and outflow fluid. The amount of fluid that leaked from the uterine cavity is difficult to measure. Once the difference reaches 1,000 ml. the operation should be concluded as soon as possible. At over 2,000 ml. the operation must be halted, the electrolytes and urea levels are to be checked and the patient should be observed for signs of pulmonary oedema. Use of Hysteromat appeared to help to reduce the amount of fluid absorbed.

The side effect of increased fluid absorption is pulmonary oedema. Diuretic drugs should be given to reduce intravascular volume and also infusion of hypertonic saline to correct hyponatraemia.

The patient can be discharged on the same day or twenty four hours following the procedure. Post operative analgesia is not usually required.

The results, in terms of satisfactory of reduced uterince bleeding are 90% of cases, with amenorrhoea in 30% and mark reduced bleeding in

40%. A return of dysfunctional bleeding occurs in about 10% of cases. This often happens when the uterus is enlarged (over 10 weeks size) or in case of adenomyosis.[6,7]

In this case the result was satisfactory. During the first three months the patient experienced normal uterine bleeding and in the following three months the bleeding was reduced to hypomenorrhoea (1-2 days) and the patient was happy with her menstruation.

Summary

We reported a case of a 38 year old Thai woman with dysfunctional uterine bleeding, who failed to respond to hormonal treatment and who was therefore treated by hysteroscopic endometrial resection. There was no complication and the result was satisfactory.

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Indicators of AIDS Prevention Among Vocational Students in Songkhla

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Abstract : *The vocational students are sexually active teenagers and also have a risk for contracting HIV infection. To predict and compare sexual behavior between male and female and to find indicators of AIDS prevention, 28-item questionnaires were obtained from 1,527 vocational students in Songkhla province. For the positive indicators, female students had significantly higher percentage ($P < 0.05$) of tendency in sexual behavior than male students in 2 items ; B1-I have as a purpose of avoiding premarital sex during studying (86.2 % V.S. 40.8 %) and B17-If you will have premarital sex and your partner will not let you use or your partner will not use condom, you will not have sex (54.6 % V.S. 29.9 %). For the negative indicators, female also had significantly higher percentage ($P < 0.05$) than male in 3 items; B14-I would be too embarrassed to carry a condom around with me, even if I kept it hidden (37.5% V.S. 33.5%), B19-You do not know how to use condom (43.6% V.S. 20.2%) and B20-You do not know how to have safe sex (42.4% V.S. 32.6%). And for the mode of experience in risk behavior, male had higher risk than female in all items, but the level of risk behavior declined from low risk to high risk. These indicated that male students will have higher risks in contracting HIV infection than female because of more risks in sexual behavior and the experience in risk behavior. Both of them showed the high level of safe sex education and awareness in AIDS prevention except for the knowledge about condom use and how to have safe sex were quite low in female students. Another concern was the risk behavior if ever put to a test of drug addict that more than 50% of male students responsed "yes". (Thai J Obstet Gynaecol 1994;6:107-116.)*

Key words : indicators, AIDS prevention, vocational students

Human immunodeficiency virus (HIV) infection is increasing over the world. In Thailand the first AIDS case was reported in October 1984[1], then infection has spread rapidly in all population. Until August 1993, the

Ministry of Public Health of Thailand reported 3,001 AIDS cases, and the incidence among teenagers aged 15-19 years was 2.2% (69 in 3,001 cases)[2]. The heterosexual transmission is the major problem and sexually active teenagers are at risk for contracting AIDS because of the high-risk sexual and drug use behavior.[3]

Adolescents are young people who are in the age of physical, mental, emotional and social development. They face various problems in adapting their transitional status to the realistic situation in the society. One of the demands of these changes is learning how to associate with opposite sex and social adjustments. Regardless of age, each adolescent boy and girl who enters a sexual relationship does so at a particular level of socioemotional and cognitive development and with whatever self-perceptions he or she has formed, as well as within a particular social and cultural context.[4] The vocational students are a group of adolescents whose lifestyles can represent other students in the same age. Their knowledge and concern about AIDS are good because they learned from the school curriculum, mass media and other sources of information, but no significant change is detected in some aspects of the level of health behavior change continuum.[5]

In the absence of a cure or vaccine for AIDS, health information and education are the most important mechanism for prevention and control of the disease. Peer and group counsellings are significant ways to raise the level of awareness, concern and preventive behavior. The study in risk and sexual behavior of the vocational students can guide and formulate the direct method to prevent the spreading of HIV infection.

Methods

The study objective is to predict sexual behavior in vocationl students and to find indicators of AIDS prevention. The hypotheses to be tested are formulated around comparison between male and female. The hypotheses are as follows :

1. Sexual behavior in male adolescents is likely higher risk than in female.

2. Tendency of AIDS prevention can be considered from many indicators of sexual behaviors and experiences in risk behavior.

The design is characterized by 2 parts of sexual behavior and risk behavior.

Materials : *Survey*

In August 1993, the study sample comprised 1,527 vocational students randomly selected. The study instrument was a 28-item questionnaire, designed to assess the students' sexual behavior and risk behavior. For the assessment, subjects were asked to response "Yes", "No", "Abstain" as follows : 22 items for tendency of sexual behavior and 6 items for experience of risk behavior.

Analytical techniques

We used simple cross tabulations items of B1-B22 and R1-R6 by sex and Chi-Square to find a significant difference to predict tendency of sexual behavior in vocational students and to level how high of risk behavior comparing between male and female.

Results

From the response of 1,527 vocational students ; 631 (41.3%) are male, and 844 (55.3%) are female. The average age is 17.59±4.04 (See table 1).

Table 1 *Frequency of male and female students and range of age (N= 1,527)*

Variables	Frequency	Percentage
SEX		
Male	631	41.3
Female	844	55.3
Abstain	52	3.4
AGE (average age = 17.59 ± 4.04)		
<14	92	6.0
15-20	1,337	87.6
21-25	79	5.2
26-30	13	0.9
>31	6	0.4

Table 1. Proportion between male and female students is nearly equivalent, and average age is 17.5 ± 4.04. Almost all students are 15-20 years old.

With comparison of sexual behavioral tendency and experience of risk behavior between male and female students, we found that there are significant differences in almost all items, except B7-I intend to protect myself by using condom (or let my partner use), B13-I feel uncomfortable buying condoms, and B14-I would be too embarrassed to carry a condom around with me, even if I kept it hidden. (see Table 2).

In this study, we put the indicators of sexual behavior into 2 parts. One consists of 14 items which show strong points of adolescents' behavior which influence sexual behavior positive indicators. Another part consists of 8 items which show weak points of adolescents' behavior which influence sexual behavior negative indicators. These indicators indicate how high of AIDS prevention. If positive indicators have high percentage, it means that the students tend to have safer sex and have higher perceiveness in AIDS prevention and vice versa.

From Fig. 1-graph of the positive indicators of male, it is evident that B1-I have as a purpose of avoiding premarital sex during studying (40.8%), B12-I discuss AIDS prevention with friend (s) (31.0%), and B17-If you will have premarital sex and your partner will not let you use or your partner will not use condom, you will not have sex (29.9%), are very low percentage. For female the low percentage items are B4-if I will have a premarital sex, my partner will be a special one for me (46.5%) and B12-I discuss AIDS prevention with friend (s) (21.2%). The noticable items, when comparing between male

Table 2 *Percentage of tendency in sexual behavior between male and female (N=1,527)*

	Behavior	Male (%)	Female (%)	P Value P<0.05=S
B1	I have the purpose of avoiding premarital sex during studying.	258 (40.8)	728 (86.2)	S
B2	I plan to have sexual intercourse before I marry.	274 (43.4)	76 (9.0)	S
B3	You think that you can commit your partner by having premarital sex.	178 (28.2)	73 (8.6)	S
B4	If I will have premarital sex, my partner will be a special one for me.	437 (69.2)	392 (46.4)	S
B5	I intentionally limit myself to have sex with one person at a time, if I will have premarital sex.	336 (53.2)	493 (58.4)	S
B6	I will make sure to have safe sex before I marry.	549 (87.0)	643 (76.1)	S
B7	I intend to protect myself by using condom (or let my partner use) when I have premarital sex	452 (71.6)	610 (72.2)	NS
B8	I intend to avoid myself from experiening any habit-forming drug.	525 (83.2)	777 (92.0)	S
B9	We should consult the doctor for premarital counseling before marriage.	501 (79.3)	733 (86.8)	S
B10	We should undergo blood tests for STD and AIDS, at premarital counseling before marriage.	511 (80.9)	741 (87.7)	S
B11	It is time for you to protect yourself from getting AIDS.	574 (90.9)	744 (88.1)	S
B12	I discuss AIDS prevention with friend (s).	196 (31.0)	179 (21.2)	S
B13	I feel uncomfortable buying condoms.	268 (42.4)	324 (38.3)	NS
B14	I would be too embarrassed to carry a condom with me, even if I kept it hidden.	212 (33.5)	317 (37.5)	NS
B15	Every time before you have premarital sex, you will make sure to have a condom for yourself or your partner.	393 (62.2)	480 (56.8)	S
B16	If you will have premarital sex and you use or (ask your partner to use) a condom, it will look like you do not trust your partner.	179 (28.3)	91 (10.7)	S
B17	If you will have premarital sex and your partner will not let you use or your partner will not use condom, you will not have sex.	189 (29.9)	461 (54.6)	S
B18	If you will have premarital sex, you will be careful of every action for having safe sex, even if people make fun of you for it	367 (58.1)	543 (64.3)	S
B19	You do not know how to use condom.	128 (20.2)	368 (43.6)	S
B20	You do not know how to have safe sex.	206 (32.6)	358 (42.4)	S
B21	If you will have premarital sex, you will make sure to use birth control in every sexual intercourse.	454 (71.9)	515 (61.0)	S
B22	Do you agree that one will lose selfcontrol when he/she gets sexually excited ?	215 (34.0)	170 (20.1)	S

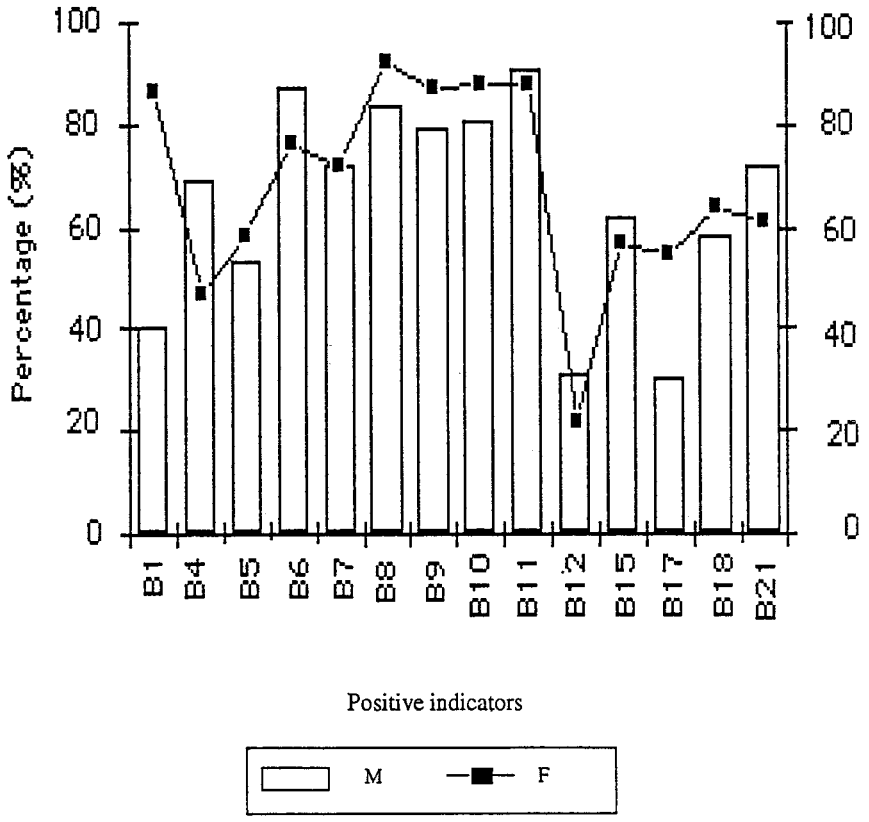

Fig. 1 Level of positive indicators (stong points of adolescents behavior which influence sexual behavior)

B1 = I have the purpose of avoiding premarital sex during studying
B4 = If I will have premarital sex, my partner will be a special one for me
B5 = I intentionally limit myself to have sex with one person at a time, if I will have premarital sex
B6 = I will make sure to have safe sex before I marry
B7 = I intend to protect myself by using condom (or let my partner use) when I have premarital sex
B8 = I intend to avoid myself from experiencing any habit-forming drug
B9 = We should consult the doctor for premarital counseling before marriage
B10 = We should undergo blood test for STD and AIDS, at premarital counseling before marriage
B11 = It is time for you to protect yourself from getting AIDS
B12 = I discuss AIDS prevention with friend (s)
B15 = Every time before you will have premarital sex, you will make sure to have condom for yourself or your partner
B17 = If you will have premarital sex and your partner will not let you use or your partner will not use condom, you will not have sex
B18 = If you will have premartital sex, you will be careful of every action for having safe sex even if people make fun of you for it
B21 = If you will have premarital sex, you will make sure to use birth control in every sexual intercourse

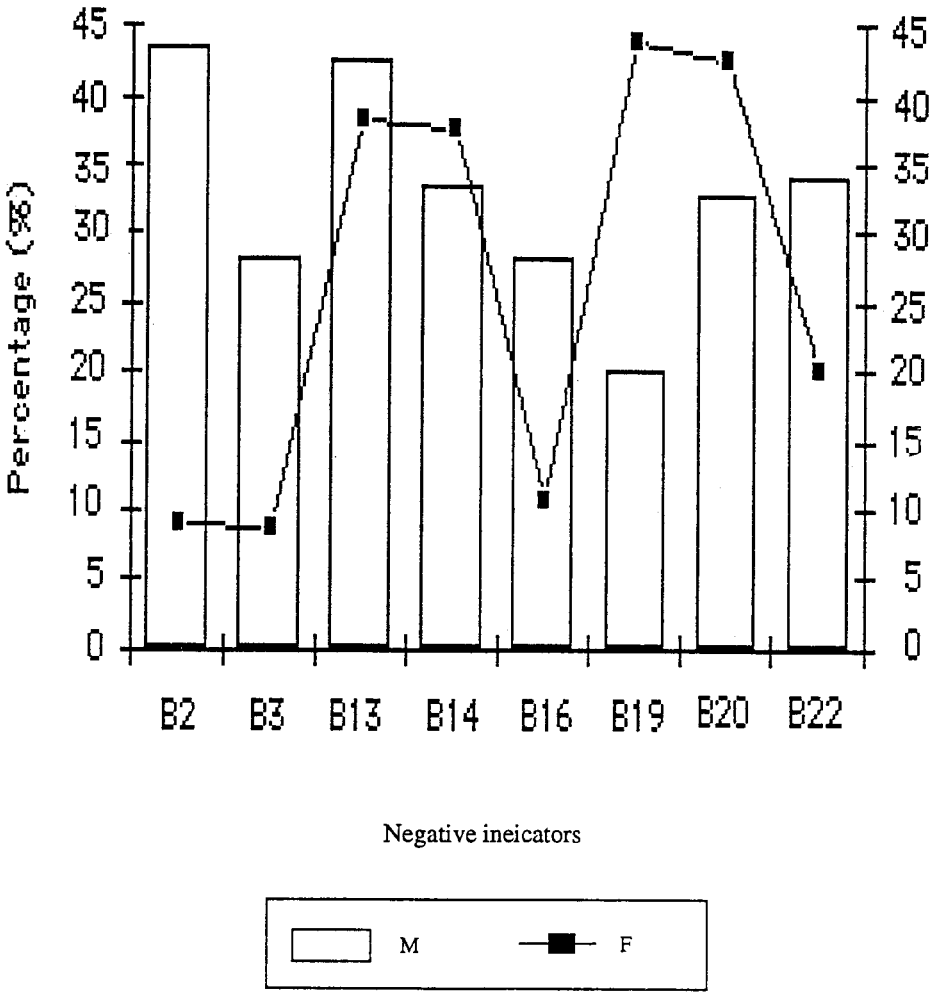

Fig. 2 Level of negative indicators (weak points of adolescents behavior which influence sexual behavior)

B2 = I plan to have sexual intercourse before marriage
B3 = You think that you can commit your partner by having premarital sex
B13 = I feel uncomfortable buying condoms
B14 = I would be too embarrssed to carry a condom with me, even if I kept it hidden
B16 = If you will have premarital sex and you use or (ask your partner to use) a condom, it will look like you do not trust your partner
B19 = you do not know how to use condom
B20 = you do not know how to have safe sex
B22 = Do you agree that one will lose self control when he/she gets sexually excited

and female, which show remarkable differences, are B1-I have as a purpose of avoiding premarital sex during studying and B17- If you will have premarital sex and your partner will not let you use or your partner will not use condom, you will not have sex, and that female have higher per-

centage than male.

From Fig. 2-graph of the negative indicators, we noticed that item B14-I would be too embarrassed to carry a condom around with me, even if I kept it hidden (F 37.5%, M 33.5%), B19-you do not know how to use condom (F43.6%, M20.2%), B20-you do not know how to have safe sex (F42.4% M32.6 %), in female are higher percentage than in male.

And it is notable between male and female in the mode experience in risk behavior and the rate of risk range from the least to the most risk. R1-Ever conduct the trial of drinking alcohol, R2-Ever put to a test of addict, R3-Ever act a forplay of sexual stimulation, R4-Ever behave of sexual intercourse, R5-Ever perform and oral sex, R6-Ever had homosexual relation. (See Table 3 and (Fig. 3)

Discussion

In recent years, many aspects regarding AIDS prevention were studied and surveyed to find the most suitable and effective mechanism. There is concern that sexually active teenagers may be at risk for developing AIDS because of their sexual practices and high rates of STDs : gonorrhea, nongonococcal urethritis, and syphilis.[6-9] Especially, slightly over 60% of the sexually active male adolescents indicated that their sexual partners were prostitutes[10-12], and the low proportions of them used condoms. This information showed the possibilities of exposure and spreading of AIDS among the adolescents and young adult population.

The Ministry of Education's strategy was originally to urge the students to learn more about AIDS via the school curriculum. The vocational students have known about AIDS in high level, but AIDS is a disease with an etiology dominated by behavioral choices. This study demonstrates that sexual behavior in male and female vocational students are much more different in almost all items, except for 3 items : B7-I intend to protect myself by using condom (or let my partner use), B13-I feel uncomfortable buying condoms, and B14-I would be too embarrassed to carry a condom around with me, even if I kept it hidden. Male students have lower percentage than female students in 2 positive indicators of sexual behavior : B1-I have as a purpose of avoiding premarital sex during studying and B17-If you will have premarital sex and your partner will not let you use or your partner will not use condom, you will not have sex. These indicate that male sexual behavior will have more risks in contracting HIV infection than female sexual behavior, but for the knowledge about how to practice safe sex like items B14, B19 and B20, male showed higher percentage than female. It may be concluded that male students are significantly influenced by Thai culture and social trend to learn and explore in sex more than female, both in right and wrong attitudes.

Table 3 *Experience of risk behavior among male and female*

Experience of risk behavior		Male (%)	Female (%)	P value (P<0.05 = S)
R1	Ever conduct the trial of drinking alcohol	515 (81.6)	425 (50.3)	S
R2	Ever put to a test of drug addict	347 (54.9)	115 (13.6)	S
R3	Ever act a foreplay of sexual stimulation	322 (51.0)	94 (11.2)	S
R4	Ever behave of sexual intercourse	273 (43.2)	67 (7.9)	S
R5	Ever perform an oral sex	87 (13.7)	49 (5.8)	S
R6	Ever had homosexual relation	48 (7.6)	26 (3.0)	S

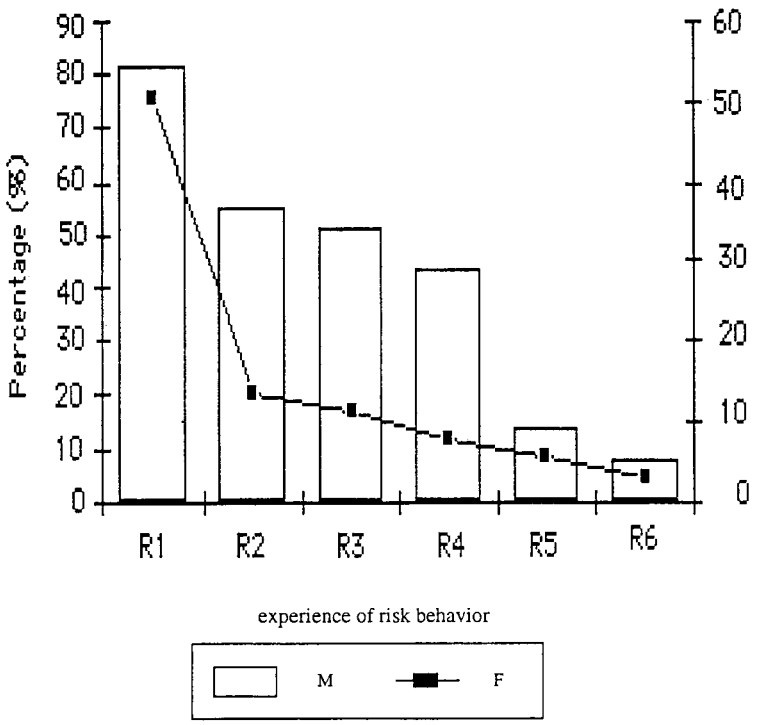

Fig. 3 Percentage of experience in risk behavior between male and female

R1 = Ever conduct the trial of drinking alcohol
R2 = Ever put to a test of drug addict
R3 = Ever act a foreplay of sexual stimulation
R4 = Ever behave of sexual intercourse
R5 = Ever perform an oral sex
R6 = Ever had homosexual relation

For some item; B12-I discuss AIDS prevention with friends, both male and female students showed low percentage (31 and 21.2%, respectively). This shows that even with more concern about AIDS prevention, the students are still reluctant and embarrassed in talking and discussing about AIDS.

The mode of experience in risk behavior and the rate of risk range from the least to the most risk (R1 to R6) were shown that male students had higher percentage than female in every item significantly. The differences confirm the hypothesis that male students had higher risk than female in contracting HIV infection, but the decline of curve from low risk to high risk behavior in both sexes showed that few percentage of students, especially female, had the possibilities to expose the disease. The other concern about risk behavior is more than half of male students ever put to a test of drug addict, though we did not ask the details of drug uses (like heroin), that can give the clearer aspect.

Most of the indicators of sexual behavior among the vocational students showed the high level of safe sex education and awareness in AIDS prevention. Unfortunately, the know-ledge about condom use and how to have safe sex were quite low in female students. It can expect to develop appropriate model or control strategies from these sexual and risk behavior for AIDS education and prevention in the vocational students.

Summary

Survey of 1,527 vocational students of Songkhla province was made to study sexual and risk behavior. Many indicators used showed difference between male and female students significantly, in nearly all items. Both sexual and risk behavior of male students were indicated at a higher risk than female in contracting HIV infection. However, most items in positive indicators of sexual behavior have high percentage. This indicates that the students tend to have safe sex and awareness in AIDS prevention. The risk behavior in some items like ever put to a test of drug addict was high in male students. This study may suggest and lead us to perform the appropriate programs for the vocational students to encourage them to change sexual behavior and attitudes, according to their risk and misunderstanding.

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Normal Pregnancy Associated with Hyperreactio Luteinalis (H.L.) : A Case Report

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Abstract : *A case of large theca lutein cysts associated with normal pregnancy is presented. The patient came to Siriraj Hospital with symptoms caused by abdominal mass during pregnancy at 14 weeks of gestation. Bilateral theca lutein cysts were suspected during laparotomy. Right salpingo-oophorectomy and left ovarian wedge resection were done. Histological finding confirmed the diagnosis to be hyperreactio luteinalis. After operation the patient went on a normal course of pregnancy. Elective Cesarean section was performed at 38 weeks of gestation and result in a normal female fetus. The etiology of theca lutein cyst in this case was unknown. (Thai J Obeset Gynaecol 1994;6:117-120.)*

Key words : normal pregnancy, hyperreactio luteinalis

Multiple theca lutein cysts are usually found in associate with hydatidiform mole and choriocarcinoma.[1,2] Beside these, this kind of ovarian cysts can be found in few cases of fetal hydrops, secondary to erythroblastosis[3], twins pregnancy[4] or ovarian hyperstimulation syndrome[1,5]. Their appearance in normal pregnancy is usually rare[4,6]. This report showed a patient with massive bilateral ovarian enlargement. The histology confirmed to be a hyperreactio luteinalis. This was found from a singleton pregnancy in the absence of any medical complications or evidences of trophoblastic disease.

Case report.

J.J., a 38 years old, married, gravida 2, abortion 1, was admitted to Siriraj Hospital on July, 31, 1992. She complained of slighty bleeding per vaginam at 14 weeks of gestation that lasted for 6 hours. The patient has previously had one spontaneous abortion a year ago at 12 weeks of gestation.

A month previously, she complained of abdominal distension, excessive enlargement of the abdo-

men, dyspepsia and dyspnea. Peptic ulcer was diagnosed. She recieved antacid and antispasmodic medication. However, there was no improvement of the symptoms. Subsequent examinations revealed an excessively enlarged and distended abdomen. The pregnant uterus was enlarged upto 14 weeks of gestation in size. A vague cystic mass was found to occupy in almost the whole abdomen. Pelvic examination revealed minimal amount of old blood in vaginal canal and a closed cervical os.

Laboratory findings were within normal limit. The serum beta-hCG was 70,000 mIU/ml. Ultrasonography showed a single viable intrauterine fetus whose size was corresponded with gestational age. A normal appearance placenta, no maternal ascites; bilateral huge multiple cystic ovaries occupying nearly the whole abdomen was also reported. Diagnosis of pregnancy with suspect ovarian tumor was made and exploratory laparotomy was done on the following day.

Intraoperative findings revealed bilateral enlargement of the ovaries with multiple cystic formation. The cysts were varied in size (Fig. 1), thin wall with clear yellow and yellowish-brown fluid content. The right ovary was 25x20 cm^2 in size. During the operation, accidental ruptured of the right ovarian cyst occured with an uncontrol bleeding, leading to unavoidable right salpingo-oophorectomy. The left ovary was 15 cm. in diametre, wedge resection was performed for the diagnosis. The uterus

Fig. 1 Gross appearance of 14 week pregnant uterus and both ovaries. The ovaries contained multiple cysts with shiny and lobulated capsular surface. The right ovary was seen to be ruptured with active bleeding.

was consistent with the gestational age at 14 weeks.

Microscopic examinations of those ovarian tissue revealed multiple follicular cysts lining by luteinized theca and granulosa cells. (Fig. 2,3).

The postoperative course was unevenful. Serum luteinizing hormone and follicular stimulating hormone levels were normal, 2.2 U/L and 5.0 U/L respectively. The patient had undergone amniocentesis for chromosome analysis at 18 weeks of gestation and revealed a normal female karryotype, 46,xx. Follow up ultrasonography were performed during 28 and 34 weeks of pregnancy. The result revealed appropriate growth of the fetus and spontaneous regression of the left ovary to a normal size. The antenatal care after that was in a normal course. Elective Cesarean section was performed at the 38 weeks of gestation due to elderly primigravidarum. A normal female infant,

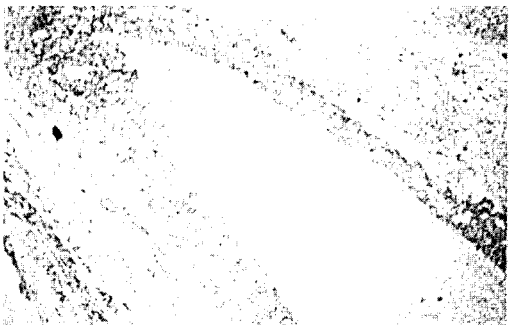

Fig. 2 Follicular cyst lined by luteinized theca interna and granulosa cell layers. (X20)

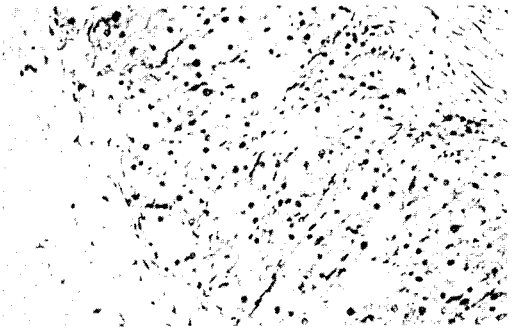

Fig. 3 Luteinzed lining cells. (X400)

weighing 3,420 gm. was born Exploration of the abdomen revealed normal left ovary. The placenta was 20x18x3 cm^3 in size and was macroscopically normal. Multiple sections of the placenta and umbilical cord were histologically normal.

Discussion

Multiple bilateral theca lutein cysts can be found in many different clinical situations. The ones that associate with hydatidiform mole, choriocarcinoma, Rh sensitization or twin pregnancy are characterized by a high incidence of elevated trophoblastic beta-hCG secretion.[1,7] In normal pregnancy, with normal hCG levels, the pathogenesis of this disease is unclear. It was believed to be caused by increasing sensitivity of ovarian stroma cells to the beta-hCG.[8]

Hyperreactio luteinalis is the pathologic term of multiple theca lutein cysts.[1] Both ovaries are usually involved. On gross inspection the capsular surface of the ovary is lobulated, smooth and shiny. Microscopic examination revealed follicular cysts with prominent luteinization of the theca interna, and also the granulosa cells in some case. The edematous stroma may also contain a large clusters of luteinized stroma cells.

The hyperreactio luteinalis may present at any stage of pregnancy, theoretically it should be found during early pregnancy, when the physiologic level of beta-hCG is high. Sometimes it may be found incidentally during Cesarean section.[4] Of these, when bilateral cystic masses were diagnosed during pregnancy, the crucial points of the managements was to recognize what the etiologies of ovarian enlargement were. The differential diagnosis included neoplastic disease of the ovaries. If the findings, either from ultrasonography or during laparotomy, are bilateral enlarged ovaries, multicystic thin wall with clear fluid content. The possibility of theca lutein cyst should be considered. Furthermore, Finding of theca lutein cyst should lead the physician to evaluate the uterine contents because of

the risk of trophoblastic disease and abnormal fetus are also very high too.[1,4,6]

This ovarian enlargement may associate with a considerable morbidity such as haemorrhage, torsion and rupture. The patient occasionally required surgery intervention for the diagnosis or management. Since this condition almost always regress spontaneously within a few weeks after parturition, so conservative management is enough for the theca lutein cyst.[1,7]

In this patient, ultrasonography revealed normal uterine content. The serum beta hCG level was appropriated to the gestational age. Laparotomy was performed for the diagnostic purposes and the resections of the large cystic ovaries were done. Unfortunately, during the manipulation of the right ovary, accidental rupture of the cyst occurred and the bleeding could not be controlled, necessitating salpingo - oophorectomy.

Conclusions

In normal pregnancy, large theca lutein cyst is uncommon. The differential diagnosis of the cause of theca lutein cyst is importance. Most of these are caused by the trophoblastic disease. The theca lutien cyst itself should be treated conservatively as it regresses spontaneously.

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Pregnancy Outcome in Ederly Women Aged 35 Years or Older

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Abstract : ***OBJECTIVE** : To compare the pregnancy complications and outcome beyond 20 weeks in women aged 35 or older with those aged 20-29. **STUDY DESIGN** : A four years retrospective cohort study from January 1, 1990 - December 31, 1993 was conducted to compare the pregnancy complications and outcome in 3334 women aged 35 or older with 6668 women aged 20-29 who were delivered in the same day. The chi-square test was used to identify trends in individual variables and outcomes. **RESULTS** : The study group had statistically significant difference in the incidence of diabetes, chronic hypertension, preeclampsia, antepartum hemorrhage, multiple gestation and preterm birth when compared with the control. Older women had Cesarean deliveries twice as often as the younger. Additionally, there was a significantly higher risks of having a low birth weight infant among women who were 35 or older (relative risk 1.30, 95% CI, 1.20-1.38). Stillbirth, perinatal morbidity and mortality were also appreciably increased. **CONCLUSIONS** : Pregnancies in women of 35 or older have higher rates of complications, Cesarean deliveries and poor perinatal outcome than those aged 20-29. (Thai J Obstet Gynaecol 1994;6:121-127.)*

Key Words : Age 35 or older, pregnancy outcome, complications, elderly

Pregnancy in women aged 35 years or older occurs with increasing frequency as more women delay child bearing resulting from dramatic changes in the social role of women, advanced education, effective means of contraception, late marriage, infertility, financial concerns, and an increasing number of working women.[1,2,3] Traditionally, pregnancies in women of advanced maternal age are considered by many authors to be high risk. Perinatal morbidity and mortality are both increased in older women.[1,4,5] Early pregnancy wastage is increased because of excessive spontaneous abortions and chromosome anomalies.[6] The incidences of preterm delivery,[4,5,7] low birth weight,[4,5,8] antepartum hemorrhage,[6,8-10] preeclampsia,[8,10] and other medical complications, i.e. diabetes and hyperten-

sion[1,2,7,10] are increased in advanced maternal age. Furthermore, the Cesarean section rate is also increased substantively in older women when compared with those who are younger.[7,9,10] Consequently, pregnancy in advanced maternal age requires high technology prenatal care, such as genetic counselling, antenatal genetic diagnosis, amniocentesis, ultrasonography, and electronic fetal heart rate testing to improve perinatal outcome[11]

The present study was conducted to compare the pregnancy complications and outcome beyond 20 weeks of gestation in women aged 35 or older with those aged 20-29 years.

Materials and Methods

A computerized perinatal data base has been set up in the Department of Obstetrics and Gynaecology, Faculty of Medicine, Chiang Mai University since January, 1990. Obstetric data including labor and delivery are recorded at the time of maternal discharge from the hospital. The study population consisted of all patients aged 35 years or older who received their prenatal care and were delivered at this institution during the period from January 1, 1990 through December 31, 1993. For comparison of each study patient, two women aged 20-29 who were delivered in the same day were recruited as the control group. The data were retrospectively analyzed from the computerized perinatal data base that included information about all patients who have given birth at this institution since January 1, 1990. Computer adapted forms which are part of the official medical record, are completed prospectively and include detailed information on the prenatal, intrapartum, and postpartum courses as well as the neonatal outcome.

Statistical analyses between groups were carried out by using either chi-square test or Student's t-test as appropriate.

Results

During the four years period, there were 29174 pregnant women who were delivered at Maharaj Nakorn Chiang Mai Hospital, of which 3334 cases were 35 years of age or older, resulting in an incidence of 11.4%. The incidence of elderly gravida had gradually increased from 8.4% in the year 1990 to 8.5%, 10.4% and 11.5% in the year 1991, 1992 and 1993 respectively. The control group consisted of 6668 pregnant patients aged 20-29 years. Among the study group 852 cases were primiparas which contributed the incidence of 25.5%. The pregnancies and their outcomes were analyzed according to four categories including pregnancy complications, intrapartum and postpartum complications and neonatal outcome.

Table 1 shows pregnancy complications compared between the two groups. There was a statistically significant increase in the incidence of diabetes, hypertension, preeclampsia and antepartum hemorrhage in the

Table 1 *Pregnancy complications*

Complications	Age 20-29 (N = 6668)		Age > 35 (N = 3334)		P-value
	No	%	No	%	
Preeclampsia	188	2.8	112	3.4	< 0.001
Diabetes	60	0.9	151	4.5	< 0.001
Chronic hypertension	42	0.6	40	1.2	< 0.001
Multiple pregnancy	49	0.7	40	1.2	< 0.001
Placenta previa	44	0.7	47	1.4	< 0.001
Abruptio placentae	15	0.2	8	0.2	< 0.05
Myoma uteri	13	0.2	18	0.5	< 0.001

Table 2 *Intrapartum and postpartum complications*

Complications	Age 20-29 (N = 6668)		Age > 35 (N = 3334)		P-value
	No	%	No	%	
Fetal distress	448	6.7	335	10.0	< 0.001
Nonvertex presentation	170	2.5	105	3.14	< 0.05
Cesarean section	924	13.8	934	28.0	< 0.001
Postpartum hemorrhage	89	1.3	52	1.6	< 0.05

older group. Moreover, myoma uteri and multiple pregnancy were also increased in the study groups.

Intrapartum and postpartum complications are described in Table 2. Fetal distress was diagnosed in 10.4% of the study group compared with 6.7% of the Control group. The older women had Cesarean deliveries twice as often as the younger. The incidence of Cesarean section was significantly higher in the elderly primigravida when compared with the elderly multigravida and the younger group. (36.5%, 25% and 13.3% respectively). Nonvertex presentation appeared to be more common in the study group. When analyzed in detail about the indications for Cesarean delivery in the study group, previous Cesarean and fetopelvic disproportion accounted for 42% and 18% respectively. While the indications for Cesarean delivery in the control group were fetopelvic disproportion (51%) and previous Cesarean (19.5%). In the elderly primigravid women, the most common indication for Cesarean delivery was fetopelvic disproportion (52%), while infertility reasons accounted for only 12%. Postpartum hemorrhage was significantly higher in the older.

Rates of preterm delivery, low

Table 3 *Neonatal outcomes*

Outcome	Age 20-29 (N = 6668)		Age > 35 (N = 3334)		P-value
	No	%	No	%	
Preterm birth	720	11.8	515	15.6	< 0.05
Lowbirth weight (< 2500)	753	11.3	529	15.9	< 0.05
IUGR*	558	8.4	315	9.5	< 0.05
Congenital anomalies	69	1.0	91	2.7	< 0.05
Macrosomia	62	0.9	34	1.0	NS
1-Min Apgar < 7	608	9.1	375	11.4	< 0.05
5-Min Apgar < 7	198	3.0	137	4.1	< 0.05
Birthweight + SD (gm)	2968 ± 518		2920 ± 613		< 0.05**
Stillbirth rate	7.0/1000 birth		9.6/1000 birth		< 0.05
Perinatal death rate	13.1/1000 birth		16.8/1000 birth		< 0.05

* IUGR = Intrauterine growth retardation
** Student's t-test

birth weight (< 2500 gm), growth retarded fetus and congenital anomalies were appreciably elevated in the group of older women (Table 3). The relative risks for preterm birth and low birth weight infants in women aged 35 or older were 1.3 (95% CI, 1.21-1.39) and 1.3 (95% CI, 1.20-1.38) respectively when compared with the risks in women aged 20-29. Low Apgar scores were more common in the study group. There were statistical differences of the stillbirth and perinatal mortality rates in the older study group when compared with the younger control.

Discussion

The present study shows that the proportion of total births in women aged over 35 is gradually increased resulting from the trends that many women are delaying childbearing. It can be seen that older women are having more babies and more older women are having.[1,6]

Pregnancy complications, both maternal and perinatal developed more often in women aged over 35. The findings of higher rates of specific antepartum complications among women who were 35 or older in this study correspond with findings in previous studie of a positive association between maternal age and preeclampsia,[4,12,13] diabetes,[2] chronic hypertension,[7,8] abruptio placentae,[6,8,13] placenta previa[6,9,13] multiple gestation,[9]) and myoma uteri.[9]

Yasin and Beydoun,[14] in a case control study, found that the incidence of "pure preeclampsia" to be about 5 percent in women in their 40s

as well as in younger control women. Reports from the Oxford Obstetric Data System observed that the incidence of preeclampsia was lower in older primigravid women.[7] It is proposed that the incidence of preeclampsia is not increased considerably as a result of advanced maternal age alone unless chronic hypertension antedates pregnancy.

The incidence of most chronic diseases increase as age advances, it is not surprising that medical complications such as, hypertension and diabetes are encountered more frequently in older pregnant women. The present study shows that the incidences of chronic hypertension and diabetes in the older increase 2-fold and 5-fold respectively when compared with the younger. Tuck and colleagues[7] observed the incidence of chronic hypertension to be nearly 12 percent in elderly primigravid women, a 3-fold increase when compared with primigravidas aged 20-25. Kirz et al[2] observed a 3-fold increase in the incidence of diabetes in pregnant women older than 35 compared with control women aged 20-25.

The incidence of late antepartum bleeding from both abruptio placentae and placenta previa, in this study, is increased in women older than 35. It seems logical that abruptio placentae is increased because of older women have a higher incidence of chronic hypertension, a major risk factor. While the risk of placenta previa increases with multiparity and advanced maternal age[1].

Although virtually all studies including this study have reported that the rate of Cesarean section increases with maternal age, the reason for this finding is not Clear.[2,4,9,10,12] No one specific indication for Cesarean birth showed an increases in pregnancies of older women. Because pregnancies in older women have been regarded as "high-risk", these may influence decision making in an attempt to reduce the risks of adverse outcomes.

The incidence of low birth weight infants is increased in women over 35 most likely because of increased preterm birth and fetal growth retardation. The incidence of low birth weight infants is increased by a factor of two in women over 35 compared with younger controls.[6] The relative risk for preterm delivery in primigravid women over 35 is increased fourfold compared with women aged 20 to 25.[7] The increased risk of preterm birth still persisted in this study when multiple gestation and placenta previa were controlled.

Rate of macrosomic babies is increased in older pregnant women when compared with younger women. This may possibly results from the same factors that cause the substantial increase in diabetes with advanced maternal age. Other common factors include large size of mothers with advancing age, maternal obesity, multiparity, prolonged gestation, and prior birth of a macrosomic baby.[1] However, Kirz et al showed that the increased rate of macrosomic babies persisted even after excluding the

diabetic mothers[2].

Congenital anomalies, Apgar scores and birth weight categories showed some age related differences. There was an increased incidence of low Apgar scores and congenital anomalies in the infants of the older pregnant women. The incidence of abnormal chromosome has been reported to increase with age in the studies from induced or spontaneous abortions, stillborns, midtrimester amniocentesis, and congenitally anomalous liveborn infants.[6] The association of age and congenital anomalies unrelated to morphological chromosomal aberrations is less clear.[15]

This study shows that both stillbirth and perinatal mortality were significantly increased in older pregnant women which agrees with reports from several investigators[4,12,16], but differs yet from others which showed no increase in either mothers with[2,10] or without such complications[12,17] when compared with the younger control. Some of these may well be related to the effectiveness of modern prenatal, intrapartum and neonatal care provided in a tertiary perinatal center.

In summary, this study has shown that pregnancies in women aged 35 or older have an increased risk of adverse perinatal outcome with higher rates of complications, Cesarean deliveries, perinatal morbidity and mortality than those aged 20 to 29.

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Simplified Hydrodissection Device

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Abstract : *The development of a simplified hydrodissection device for use during operative laparoscopy is described. The device used mechanical-pneumatic operation, with CO_2 propellant gas and consists of control unit, fluid warmer system and irrigation/suction probe. The irrigation pressure is adjustable throughout a range of 100-760 mmHg and the flow rate ranges from 690 to 1,400 ml/min. The performance of the device using a commercial irrigation probe (maximal flow rate of 2,258 ± 28 ml/min at 760 mm Hg pressure) is comparable to a commercial irrigation device. For suction, the wall suction system is used. The device has been used in 20 operative laparoscopy cases, and is found to be cost effective, simple to operate, having a continuous high pressure flow rate and delivering homeothermic solution. The major defect that needs further development is in the locally made irrigation probe. (Thai J Obstet Gynaecol 1994;6:129-139.)*

Key words: hydrodissection, aquadissection, irrigation/suction device, laparoscopic surgery

Operative laparoscopy is being used for an increasing number of intra-abdominal procedures. Integral parts of most of these procedures are irrigation, hydrodissection with physiologic solutions (such as normal saline or lactated Ringer's solution) and suction[1-3]. Hydrodissection is a technique that makes use of hydraulic energy to facilitate separation of tissue planes with less trauma than if the maneuvers were carried out by mechanical means. Modern hydrodissection devices consist of adjustable hydraulic pressure at a relatively high flow rate with a fluid warmer system. Elaborated and sophisticated design has led to accuracy and simple operation, but at the expense of high capital and maintenance costs[3,4]. Many devices have been manufactured without a fluid warmer system, so the use of these high flow systems, especially during lengthy cases, may result in the use of a significant volume of hypothermic fluid. Because aqueous medium is an excellent coolant, this may contribute to the hypothermia which was reported to occur during some cases of operative

laparoscopy[5].

The Aqua-purator (WISAP, Sauerlach, Germany) was the first of the high pressure irrigation/hydrodissection devices[1]. It delivers fluid under 170 mmHg pressure at a rate of 1,500 ml/min without irrigation fluid warmer system. Recently, a nonelectric CO_2 powered irrigation system was introduced (CO_2 HYDROMAT, Karl Storz CO, Tuttlingen, Germany), in which the irrigation pressure can be varied between 0 and 800 mmHg. This device has an irrigation fluid warmer system as an accessory. Laparoscopic irrigation using a prewarmed pressurized system was reported by Hurd et al[4]. This device was originally designed to deliver large volumes of homeothermic (37° C) fluid quickly to trauma and burn patients. The irrigation pressure is 300 mmHg, and the flow rate is approximately 650 ml/min. All these products are relatively expensive(more than US$4,000)[4]. In our Department, we have used an Endo-irrigator integrated in Endo-Surgery CO_2-Pneu (Richard Wolf, Knittlingen, Germany) with a Storz irrigation/suction probe (Karl Storz CO, Tuttlingen, Germany).

We have designed a simplified hydrodissection device that has low cost and possesses many desirable features, such as adjustable hydraulic pressure, fluid warmer system, valves and lumens of a strong dissection probe that were not easily obstructed, and simplicity in use. The device can be constructed and maintained locally, using available local materials.

Materials and Methods

Function and design[6,7]

The simplified hydrodissection device uses mechanical-pneumatic operation with CO_2 propellant gas. Figure 1 shows the block diagram of the device, consisting of pressure delivery unit with warmer and irrigation/suction probe. High-pressure gas from CO_2 cylinder is reduced with a pressure regulator. The system pressure is adjustable throughout a range of 100-760 mmHg (2-15 psi) and is displayed on the low-pressure gauge. Low-pressure gas is delivered to a solenoid valve which can be activated by a footswitch. Then gas passes through a flow-limiting valve that will cut off gas flow if the flow rate is more than 3 l/min, to prevent insufflation of high-flow propellant gas into the peritoneal cavity when the irrigation fluid bottle is empty. The irrigation fluid used is in a one-liter glass bottle with a trocar puncture cap. The glass bottles can tolerate pressure up to 100 psi according to Thai Industrial Standard (TIS 532-1984). Two fluid bottles can be simultaneously connected to the device, and are placed on the warmer to maintain the fluid temperature. A three-way valve is used to select the fluid bottle. The propellant gas is delivered to either fluid bottle via two silicone tubes connected to the pressure trocar by Luer-lock. A long sterile silicone irrigation tube with Luer-lock end is used to attach an irrigation trocar to the

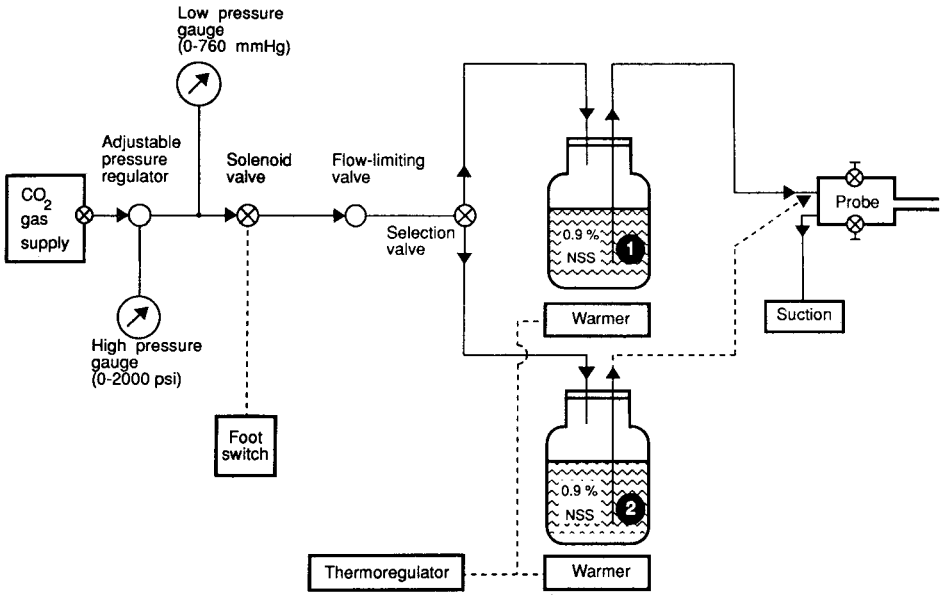

Fig. 1 Block diagram of the simplified hydrodissection device. (NSS : normal saline solution)

irrigation/suction probe. The probe has two trumpet valves, but a single channel for irrigation and suction to maximize irrigating and suctioning capacity. For suction, the wall suction is used. This device is designed to comply with the International Electrotechnical Commission(IEC 601-1:1988) for Class I equipment, and meets the appropriate current leakage requirements.

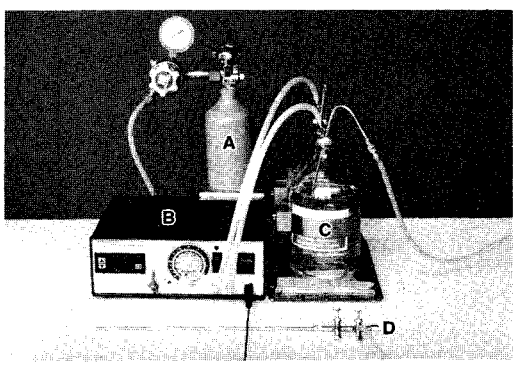

Fig. 2 Prototype of the simplified hydrodissection device. (A : CO_2 cylinder with pressure regulator, B:control unit, C:warmer with two bottle holders, D:locally made irrigation/suction probe)

Description of prototype

The prototype of the simplified hydrodissection device essentially consisted of a one-liter CO_2 cylinder with pressure regulator (Fig. 2-A), control unit(Fig. 2-B), warmer with two bottle holders (Fig. 2-C), and irrigation/suction probe (Fig.2-D). A Model 101 Harris CO_2 pressure regulator (Harris Calorific CO, Cleveland, OH, USA) consisted of high-pressure gauge (0-2,000 psi) to display the pressure in CO_2 cylinder, and a pressure control knob, rotated to adjust the

pressure in the system. Clockwise rotation of the knob increased system pressure and anti-clockwise rotation decreased system pressure. The adjusted pressure was displayed in mmHg by the low-pressure gauge. A solenoid pneumatic valve was used to control propellant gas. The flow-limiting valve was modified from the inner tube of a Rotameter used for oxygen therapy (Ohmeda, Columbia, MD, USA). This was out of use because the outer tube has been broken. The inner tube could tolerate pressure up to 50 psi. If the propellant gas flow was over 3 l/min, when the fluid bottle was empty, the ball of the flow-limiting valve would be pushed up to block the gas flow to less than 1 l/min. The usual irrigation fluid used was 0.9% normal saline solution (USP XXII) in a one-liter glass bottle, that could be prepared by the Pharmacy Department of Songklanagarind Hospital. The warmer with two bottle holders was constructed from a stainless steel plate, 1 mm thick. Two insulated heater were placed in the waterproof warmer tray and the maximum power was about 60 W. A Model MC311 Thermoregulater (SAE, PN,Italy) with thermostat differential of 0.2° C was used to control the warmer temperature. The pressure trocars were 14 gauge stainless-steel needles of 1.5 mm internal diameter (ID) and 51 mm in length. The irrigation trocars with Luer-lock end were constructed from locally available standard brass tube, 4.70 mm outer diameter (OD), 3.40 mm ID and plated with nickel. The irrigation/suction probe consisted of the body with two trumpet valves and irrigation/suction cannula, 295 mm in length(the same size as the irrigation trocar): all parts were constructed from standard brass tube and plated with nickel. The lumen of each trumpet valve was only 3 mm(smaller than that of irrigation/suction cannula), because of the limitations of the available standard brass tube(7.35 mmID) used as valve cylinder. For suction, the Ohmeda Suction System (Ohmeda, Columbia, MD, USA) with 3,000 ml bottle mounted on a stand and connected to wall suction, was used. The components and costs of the prototype are shown in Table 1.

Operating instructions

After turning on the main switch, the thermoregulator is set at 55° C and the warmer is switched on. Two one-liter irrigation fluid bottles, prewarmed to about 37° C, are placed in bottle holders on the warmer. Pressure trocars and irrigation trocars puncture each bottle cap by sterile technique. Each propellant gas tube is connected to the pressure trocar of each fluid bottle. The long sterile silicone irrigation tube with Luer-lock end is used to attach the irrigation trocar of bottle I to the irrigation valve of the probe. Before the CO_2 cylinder valve is turned on, the pressure control knob is rotated anti-clockwise until it moves freely. When the CO_2 cylinder valve is

Table 1 *Simplified hydrodissection device components*

Components	Price (Baht)
One-liter CO_2 Cylinder	1,400
Pressure regulator with high-pressure gauge	1,350
Solenoid valve	550
Flow-limiting valve	300
Low-pressure gauge (0-760 mmHg)	2,000
Selection valve + connector	600
Footswitch + cable + case + circuit	500
Thermoregulator unit	2,700
Warmer with 2 bottle holders	1,000
Pressure and irrigation trocar	200
Locally made irrigation/suction probe	1,800
Silicone tube (4.85 mm ID,8.70 mm OD) 5 meter	535
total cost	12,935 Baht (US$520)

turned on, the high-pressure gauge will show pressure in the cylinder. Then the pressure control knob must be rotated slowly clockwise, so that propellant gas pressure will show on the low-pressure gauge in mmHg, until the desired system pressure is reached. Once the system pressure is set, the pressure will almost constant and require only a little adjustment in subsequent use. Low system pressure (100-300 mmHg) is used for irrigation, while high system pressure (300-760 mmHg) is used for tissue dissection. The selection valve is turned to bottle I position. The sterile silicone suction tube is connected to the suction valve of the probe. Now the device is ready to use, fluid will flow out of the irrigation cannula of the probe when the footswitch and irrigation trumpet valve of the probe are simultaneously pressed. When bottle I is empty, the procedure can be continued quickly by turning the selection valve to bottle II position and changing the irrigation silicone tube from the irrigation trocar of bottle I to that of bottle II.

Instrument tests

Both laboratory and clinical tests were carried out to assess the performance of the prototype. We determined the maximal flow rate produced by the prototype for different irrigation pressures (100-760 mmHg) and for different irrigation probes (locally made irrigation probe versus Storz irrigation probe). The performance of the prototype using locally made and Storz irrigation probe were then compared with the Endo-irrigator using either probe and the Stewart system[3] at the same irrigation pressure (150 mmHg). The Stewart system in this study consisted

of the routine intravenous tube and fluid suspended at a height of six feet. The flow rate at the tip of the irrigation probe was measured using a Model 22G02 Urodyn1000 Uro flowmetry connected to a Model 22K10 Uroflow Transducer (Dantec, Skovlunde, Denmark). All the flow rates represented the maximal flow rate obtained.

The efficiency of the fluid warmer system was assessed at maximal warmer setting (55°C) at room temperature (24° C). The prewarmed (37° C) and room temperature fluid in one-liter glass bottles were placed on the warmer, and the changes of fluid temperature were compared with those of the prewarmed(37°) fluid in one-liter glass and plastic bottle without warmer. We used a Temperature recorder (Amprobe Instrument, NY, USA) to evaluate changes of fluid temperature.

The clinical performance was assessed by surgeons and operating room staff. This instrument has now been used satisfactorily during twenty elective and emergency operative laparoscopy cases.

Data points in all laboratory tests represent the results of ten measurements. The data obtained are presented as mean ± SD and do not conform to a normal distribution, so Mann-Whitney U test has been used to assess differences between the groups and the significance of difference was $p< 0.05$. To determine a correlation between the irrigation pressure and flow rate, a linear regression analysis of the data has been performed.

Results

The maximal flow rate of the prototype using locally made irrigation probe at a maximal irrigation pressure(760 mmHg) was 1,456±25 ml/min. When the prototype used the Storz irrigation probe, the flow rate increased to 2,258 ± 28 ml/min. The correlation between irrigation pressure (100-760 mmHg) and flow rate(ml/min) using either locally made or Storz irrigation probe was linear. The linear regression was formulated for each probe. The flow rate of the locally made probe was 546 ± 1.16 (pressure) and the flow rate of the

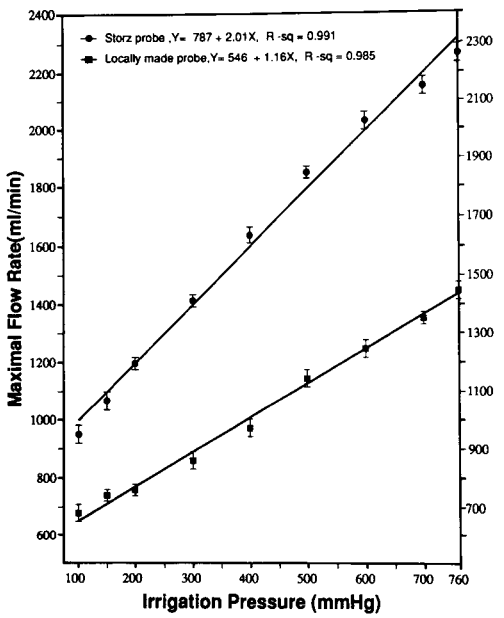

Fig. 3 The correlation between the maximal flow rate and irrigation pressure obtained with locally made (■) and Storz (●) irrigation probe.

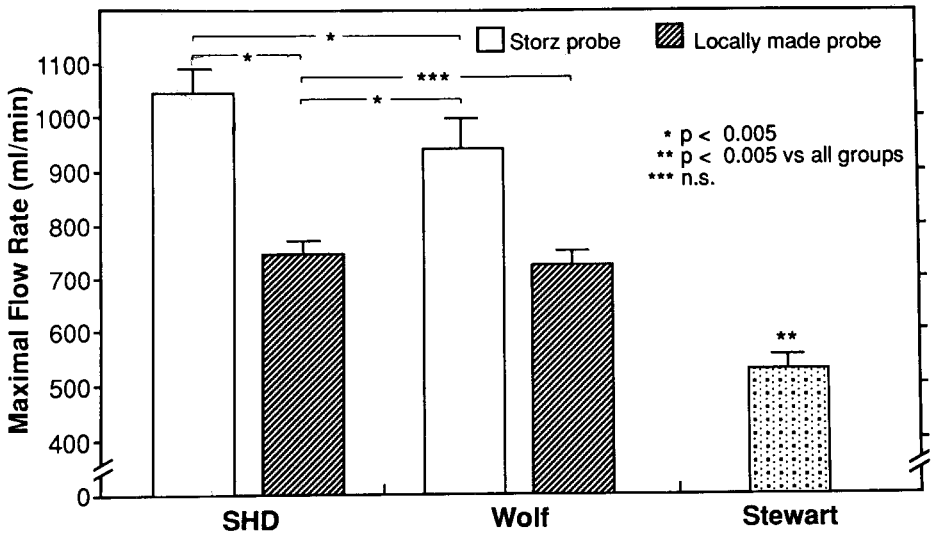

Fig. 4 Comparison of the maximal flow rate obtained with the simplified hydrodissection device(SHD) and Endo-irrigator (Wolf) using locally made or Storz irrigation probe, and the Stewart system at the same irrigation pressure(150 mmHg). (*P<0.005,P<0.005 vs all groups,***no statistical significance)**

Storz probe was 787±2.01(pressure) with R-squared of 0.985 and 0.991 respectively (Fig.3).

Fig. 4 shows the performance of the prototype (SHD) with Endo-irrigator(Wolf) and the Stewart system at the same irrigation pressure (150 mmHg). The prototype using locally made irrigation probe has a flow rate less than that obtained by the Endo-irrigator using the Storz irrigation probe (Wolf/Storz system) [743 ± 11 vs 941 ± 58 ml/min, p<0.005]. When assembled with the Storz irrigation probe, the prototype had a flow rate increase to 1,043 ± 43 ml/min, significantly highter than the Wolf/Storz system (P<0.005). The flow rate of the prototype using the locally made irrigation probe was comparable to the Endo-irrigator using the locally made irrigation probe (743 ± 11 vs 726 ± 20 ml/min, P = 0.09). Both the prototype and Endo-irrigator using either probe had a flow rate higher than that of the Stewart system (524 ± 12 ml/min, P<0.005), and the flow rate of the Stewart system decreased rapidly, needing frequent inflation of the pressure cuff to maintain the flow rate.

There was some leakage of the irrigation fluid from the valve of the locally made irrigation probe during use both with the prototype and the Endo-Irrigator. The suction capacity using the locally made irrigation/suction probe at maximal suction pressure (-400 mmHg) was approximately 1.5 l/min.

The changes of the fluid temperature in the laboratory test of the warmer of the prototype are shown in Fig. 5. The warmer heated the room temperature (24° C) fluid very slowly

Table 2 *The specifications of the simplified hydrodissection device*

Irrigation pressure	760 mmHg (max)
Instillation capacity	1.4 l/min (max)
Vacuum pressure	-400 mmHg (max) (depends on wall suction)
Suction capacity	1.5 l/min (at max vacuum pressure)
Mains voltage/Fuse	220 Vac, 50 Hz/ 0.5 A
Warmer	60 W (max)
Irrigation fluid	0.9% NSS in one-liter standard glass bottle (TIS:532-1984)
Dimensions	42 cm x 13 cm x 31 cm (wxhxd; not including CO_2 cylinder)
Weight	5.5 kg (not including CO_2 cylinder)

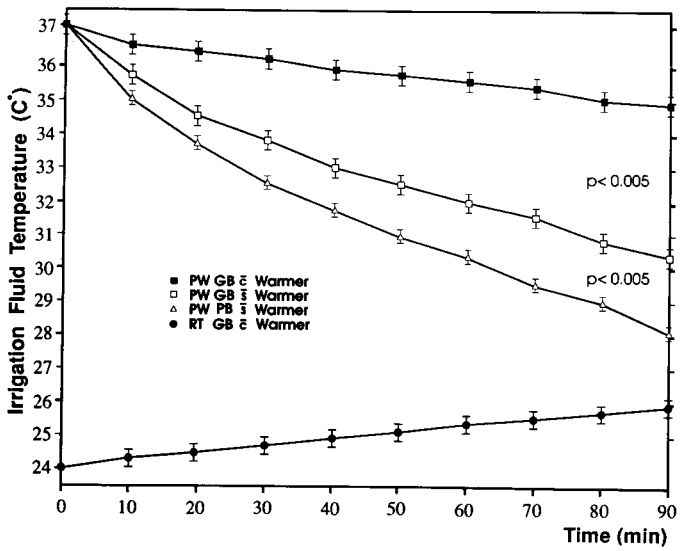

Fig. 5 Effect of the warmer on the irrigation fluid temperature. The irrigation fluids were prewarmed (37°C) fluid in glass bottle with warmer (■: group I), prewarmed fluid in glass bottle without warmer (□: group II), prewarmed fluid in plastic bottle without warmer (Δ: group III), room temperature(24°C) fluid in glass bottle with warmer (● :group IV). The prewarmed fluid group II cooled down significantly compared with group I (P<0.005) and group III cooled down more rapidly than group II(P<0.005), both after 10 minutes.

(approximately 1° C/h), whereas for the prewarmed (37° C) fluid, the warmer minimized the cooling down of the fluid temperature. When the warmer was not used, the prewarmed fluid temperature decreased rapidly compared with the fluids using the warmer (P<0.005) and there was significant reduction of the fluid temperature in the plastic bottle compared with the glass bottle (P<0.005) after ten minutes. The specifications of the prototype are shown in Table 2.

The prototype was as useful

surgically as the Wolf/Storz system during fifteen cases of elective operative laparoscopy and five emergency ectopic pregnancies managed by laparoscopic salpingectomy or salpingo-oophorectomy. The fifteen cases of elective operative laparoscopy inclunded ten cases of adnexal cysts managed by salpingo-oophorectomy or cystectomy, two cases of laparoscopic hysterectomy and three cases of pelvic endometriosis managed by lysis adhesion and laser vaporization. There was no appreciable drop in the patients' temperature and no postoperative shivering after 2-4 liters of irrigation.

Discussion

Irrigation is an integral part of surgery performed by either laparotomy or laparoscopy. In contrast to laparotomy, where the use of warmed irrigation fluid is routine[8], irrigation fluid used during laparoscopy is often at room temperature. In other endoscopic procedures where large volumes of room temperature (21° C) fluid are used, such as transurethral prostatectomy, significant cardiac stress has been attributed to rapid cooling of the patient[9]. Because hypothermia is a real risk during lengthy laparoscopic procedures[5,10], the use of warmed irrigation fluid may be advantageous for laparoscopy as well. One common approach to this problem is the use of prewarmed containers of solution pressurized for irrigation by various methods[3]. However, the actual temperature of the fluid reaching the patient may vary widely depending on the initial temperature of the fluid, the length of time the fluid container is exposed to room temperature before use, and the type of container. Fluid that is too warm (>37° C) may actully increase the risk of postoperative adhesion formation[11]. Conversely, fluid that is allowed to cool before use offers little advantage to the patient, and from this study the plastic bottle cooled down more rapidly than the glass bottle. So we designed a method of using prewarmed fluid at 37° C in a glass bottle normally used for laparotomy, and a warmer system to reduce the cooling down of the fluid. A fluid warming system that can warm up room temperature fluid quickly is sophisticated and costly.

The flow rate of the prototype using locally made irrigation probe ranges from 690 to 1,400 ml/min. The flow rate at 150 mmHg pressure is significantly higher than that achieved by the Stewart system[3], and remains constant during the irrigation period. Although this rate is not as high as the rates of up to 3,000 ml/min possible with some commercial irrigation units (Cabot Medical, PA, USA)[4], flow rates and pressure obtained with the prototype are more than adequate for rapid irrigation and hydrodissection during operative laparoscopy.

The three major defects of the prototype are in the locally made irrigation probe and flow-limiting valve. First, the internal diameter of

the irrigation cannula is smaller than that of the commercial irrigation probe. Second, there is some leakage of the irrigation fluid at the valve, which explains why the constant and slope in the formula of the locally made irrigation probe are less than those of the commercial irrigation probe. Third, the flow-limiting valve cannot cut off but only decrease propellant gas flow to 1 l/min instead of over 15 l/min when the fluid bottle is empty.

The setup and operation of the prototype is remarkably simple. Once both the system pressure and the warmer are preset, it rarely requires adjustment. The irrigation fluid in a one-liter glass bottle can be prepared locally by the Pharmacy Department of most hospitals: the cost is low and it can reduce the wast of disposable plastic fluid bottles.

As with any new technology, the cost per case should be considered. Because this simplified device has an initial cost of only 13,000 Baht (US$ 520) and the irrigation fluid costs only 10 Baht (US$ 0.4) per liter, it is therefore extremely cost effective.

Our initial clinical experience suggests that the prototype of the simplified hydrodissection device performs well. However, this device is at the prototype stage and there are certain aspects which need further development. These include a high efficiency probe which has an accessory channel for electrosurgery or laser surgery, a good heat-conducting warmer and a flow-limiting valve that can completely cut off the propellant gas flow.

In conclusion, this paper has shown that the simplified hydrodissection device for operative laparoscopy is effective, simple to operate, having a continuous high-pressure flow rate and delivers a homeothermic solution. It is a very cost-effective and appropriate piece of technology for developing countries.

Acknowledgements

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Polycystic Ovary Syndrome (PCOS) : An Overview

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Abstract : *PCOS is a common gynecological disorder. While the etiology of this condition is still unknown, several abnormalities involving the pathophysiology of this syndrome have been demonstrated. Diagnosis of PCOS usually relies on clinical, biochemical and ultrasonic appearance of the ovary which is not difficult in most cases. Apart from suffering from menstrual disturbances, androgenic symptoms and infertility, if left untreated, this patient has high risk of developing endometrial hyperplasia and carcinoma, breast cancer, diabetes mellitus, hypertension and cardiovascular disease. Several therapeutic options are now available. For those who do not immediately desire pregnancy, treatment with combined oral contraceptives or progestogen is usually effective. For infertile women, ovulation induction, medically, is successful in most cases. Surgical treatment (cauterization of small peripheral cysts) is another alternative in selected case. (Thai J Obstet Gynaecol 1994;6:141-148.)*

Key words : polycystic ovary syndrome, pathophysiology, consequences, diagnosis, treatment.

The historical aspect of PCOS is dated back to 1935 when Stein and Leventhal reported patients with amenorrhea, hirsutism and enlarged polycystic ovaries. The so-called Stein-Leventhal syndrome[1] was subsequently shown to have wide range and spectrum of clinical, biochemical and pathological findings. The term "Stein-Leventhal syndrome" is rarely used at present and is replaced by polycystic ovary syndrome (PCOS).

PCOS is a common gynecological disorder. It is not a disease but a heterogenous clinical syndrome. The main characteristics of (PCOS) are chronic anovulation (abnormal gonadotropin secretion) and hyperandrogenemia. Chronic anovulation accompanying hyperandrogenemia however, are not always diagnostic for PCOS. These conditions can be found in several clinical situations such as Cushing's syndrome, late onset congenital adrenal hyperplasia, virilizing ovarian and adrenal tumor, hyperprolactinemia, thyroid dysfunc-

tion and obesity. These groups of patients are sometime called the syndrome of hyperandrogenism and chronic anovulation[2].

Etiology

The etiology of PCOS is still unknown. Several investigators have demonstrated the abnormalities involving the pathophysiology of this syndrome, including hypothalamic dysfunction, enzymatic abnormalities in the adrenal gland and ovary, and hyperinsulinemia. The relationship between various factors regulating ovarian function and development of PCOS have also been explored, such as gonadal peptides, several growth factors and renin angiotensin system. At present, several groups are interested in the role of insulin/insulin-like growth factors (IGFs) and insulin-like growth factor binding protein (IGF-BP) on PCOS[3]. However, the definite cause of PCOS remains unsettled. Since the clinical symptoms in most patients start around puberty, it has been suggested that the abnormality should begin at that period when the maturity of hypothalamic-pituitary-ovarian axis is not fully reached[4]. Peripubertal hormonal changes are also similar to the pattern found in patient with PCOS in many aspects[3].

Pathophysiology

While the etiology of PCOS remains unknown, the pathophysiology of this disorder has been illucidated, although not fully. Chronic anovulation leads to unopposed estrogen production which increases gonadotropin releasing hormone (GnRH) pulsatility. The event results in an increase of both amplitude and frequency of luteinizing hormone (LH). Follicle stimulating hormone (FSH), however, is usually normal or decreased, due to the negative feedback effect of estrogen. The sustained high LH level causes stimulation of theca cell function to secrete androgens (testosterone, androstenedione). The ovarian androgen production is also augmented by hyperinsulinemia and increased action of IGFs. Adrenal glands also play role in hyperandrogenemia in PCOS[4]. Decreased FSH and increased androgen levels inhibit follicular growth, therefore, ovulation doesn't occur. Without ovulation, the patient is in the vicious cycle of unopposed estrogen status. Total estrogen production in PCOS is the sum of estrogen from multiple tiny follicles and the peripheral conversion from androgen. This extraglandular source accounts for a significant portion in obese patients. In PCOS, level of sex hormone binding globulin (SHBG) and IGF-BP is lower than normal. Therefore, the level of free portion and the action of androgen as well as estrogen are increased.

Pathology

Polycystic ovary (PCO) is an anatomical term defining the ovary

with numerous small cysts. In typical cases, both ovaries are slightly enlarged with smooth thickened avascular white capsule. Cut section of the ovary reveals multiple subcapsular follicular cysts, diameter about 4-8 mm. Hyperplasia of theca-stromal cell is characteristic[5,6]. However, not all patients with PCOS has PCO. Some patients have normal sized ovaries or unilateral enlargement. In another aspect, PCO can also be found in other conditions apart from PCOS. This makes the diagnosis of PCOS sometime confusing.

Prevalence

The prevalence of PCOS is difficult to establish. It is the most common cause of estrogenic anovulation and hirsutism. It has been estimated to affect as much as 5 percent of the female population[7]. By using ultrasonic criteria, PCO was found in 32 percent of women with secondary amenorrhea, 87 percent of oligomenorrhea, and 87 percent of hirsute women who had history of normal menstruation[6]. In Ramathibodi's study, the prevalence of PCOS in women presenting with acne was about 37 percent[8].

Diagnosis

The diagnosis of PCOS at present relies on clinical, biochemical and ultrasonic features[4,6,7,9]. The wide clinical spectrum of PCOS is the results of chronic anovulation (menstrual disturbances and infertility) and hyperandrogenemia. Several forms of menstrual disorders are observed in these patients i.e. amenorrhea, oligomenorrhea, dysfunctional uterine bleeding, menorrhagia and metrorrhagia. The symptoms begin at peripubertal period in most cases. Infertility is also a common presenting symptom in married women. However some patients experience sporadic ovulation and subsequent spontaneous pregnancy does occur. In PCOS, only mild to moderate degree of hyperandrogenism are presented which lead to cosmetic problems such as acne and hirsutism. Severe degree of androgenic symptom, such as clitormegaly, is rare. In Thai patients, the prominent androgenic symptoms are acne and seborrhea. Hirsutism, in contrast to the patients in western countries, is less common. Degree of hirsutism does not depend only on the androgen level but also on the sensitivity of the pilosebaceous unit to androgen. Asian women are generally less hirsute than the Caucasian. Obesity is also common. In the severe cases, hyperpigmentation in the neck region, axilla and breast fold (acanthosis nigricans) may also be presented. Pelvic examination may reveal bilateral ovarian enlargement in some cases.

The common hormonal changes in PCOS are elevated level of LH and low or normal FSH. The LH to FSH ratio is raised more than twice. However, in some cases elevated LH/FSH could not be demonstrated mainly due to the pulsatile nature of

LH secretion. Due to the inconsistent finding, some groups have abandoned the LH to FSH ratio as a diagnostic criterion for PCOS[10]. While serum LH may not be increased in some patients, the bioactive LH was found to be elevated in almost all cases[11]. The bioactive LH assay at present, however, is not available for routine test. Serum androgens are elevated. Total testosterone is increased but usually not more than 1.8 ng/ml. Serum dehydroepiandrosterone sulfate (DHEAS), adrenal androgen, is also mildly elevated (<700 ug/dl). Mild to moderate rise of prolactin level may be observed in about 1/3 of the cases[12].

During the last decade, the development of high resolution ultrasonography enables gynecologists to use it in a non-invasive study of the ovarian morphology. The typical ultrasonic findings of PCO are slightly enlarged ovaries with multiple sonolucent cystic structures along the periphery and dense echogenic stroma (Fig. 1). Vaginal ultrasound is preferable to the abdominal route in this aspect[6,13].

Late consequences

PCOS is a syndrome which should receive great concern from both the patients and physicians. Apart

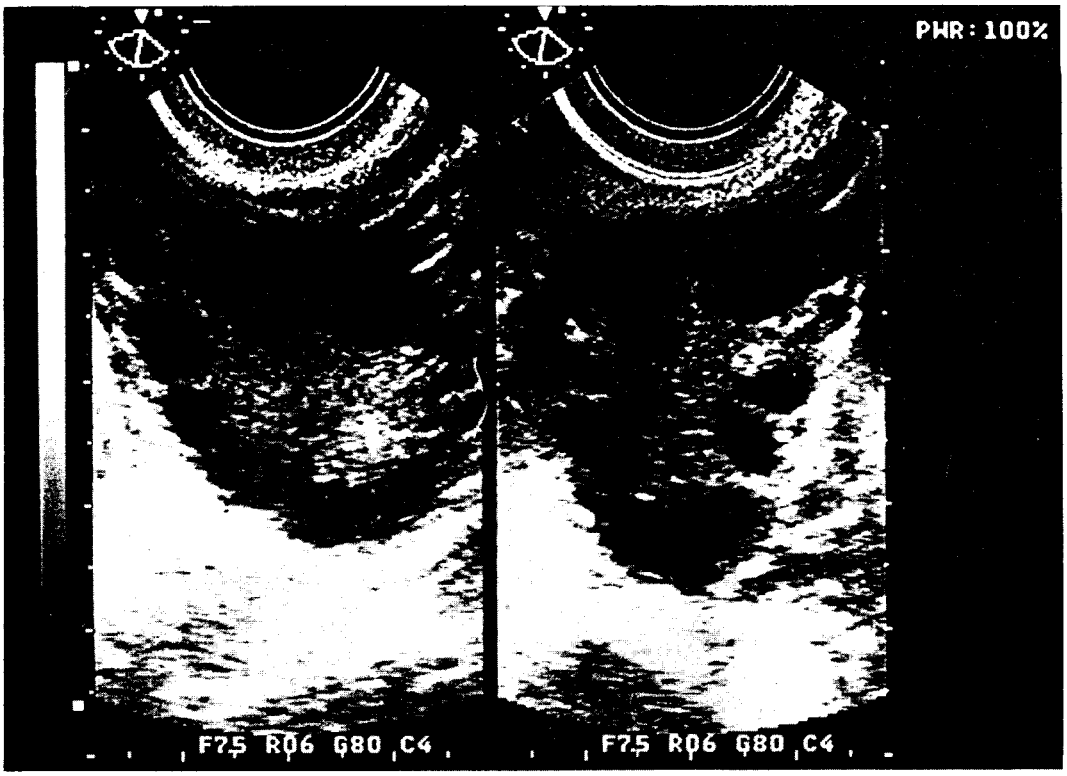

Fig. 1 Transvaginal ultrasonic appearance of the polycystic ovary in PCOS patient.

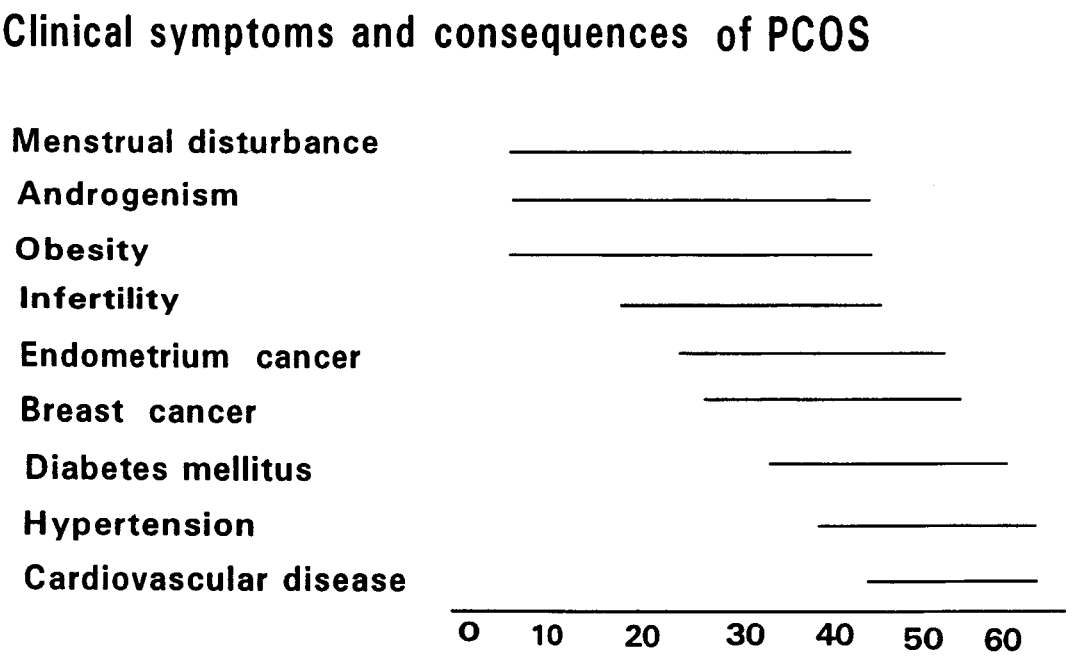

Fig. 2 Purposed consequences of PCOS in relationship to the age of patient (year).

from the clinical problems above, if left untreated, the patients have high risk of developing endometrial hyperplasia and carcinoma, breast cancer, diabetes mellitus, hypertension and cardiovascular disease[14-17]. The purposed development of these consequences is shown in Fig 2. The predisposing factors of these late consequences in PCOS patient include obesity, abnormal lipid profile and increased insulin resistance. These potential sequelaes should alert the physician for early diagnosis and treatment of this disorder.

Treatment

Since the pathogenesis of PCOS remains unclear, the preventive measure has not been established. However, there are considerably effective therapeutic strategies for these patients. The management generally depends on patients' problems and their desire of pregnancy. In those who want to become pregnant, ovulation induction should be considered[7,18]. Clomiphene citrate remains the first line ovulation inducing agents. The addition of dexamethasone to suppress adrenal androgen may be advantageous in some cases. Patients with elevated prolactin level may benefit from dopamine agonist. Ovulation could be acheived in almost 80 percent of the patient. Pregnancy, however, occurs in about half. Human menopausal gonadotropin and pure FSH are more effective in induction of ovulation and pregnancy but more costly. During the treatment

course, the patients should be closely monitored to avoid the serious complications, including ovarian hyperstimulation syndrome and high ordered multiple pregnancy. Using the threshold principle, low dose FSH (step up) therapy could effectively induce monofollicular development, avoiding such complication. Another problem frequently occurred during gonadotropin treatment in PCOS is premature luteinization, which can be found in 20-30 percent of cycles. The introduction of gonadotropin releasing hormone agonist (GnRHa) which suppress endogenous LH leads to dramatic decrease of this problem. At present, the combination of GnRHa and gonadotropin appears to be the most effective method of ovulation induction in PCOS patients.

For PCOS patients who do not wish to become pregnant immediately, the treatment should aim to interrupt the vicious cycle of this disorder. Progestogens alone induce regular endometrial shedding and decrease androgenic symptoms. More effective therapy could be accomplished by the use of combined oral contraceptive, (OCs) containing estrogen and progestogen[4,14,19]. There are several therapeutic advantages of using combined OCs in women with PCOS. Cyclic shedding of endometrium results in regular cycle, thus prevents endometrial hyperplasia and cancer. Improvement of androgenic symptoms is usually observed during OCs treatment. Progestogens suppress LH secretion effectively, thus lessen theca cell activity. Estrogen increases sex hormone binding globulin (SHBG) level, thus decreases free testosterone fraction. The amount of estrogen in low dose OCs is enough to cause this effect. OCs also decrease DHEAS, an adrenal androgen, but the exact mechanism is not known, Recent studies have also shown that OCs have decreasing effect on IGF-I and increasing IGFBP-I which result in reduction of ovarian androgen production. Other than the above properties, OCs also inhibit binding of dihydrotestosterone (DHT) to androgen receptor. In PCOS patient recieving OCs, the improvement of acne and oily skin are usually achieved within the first few cycles, but the clinical effect on hirsutism takes about 6 to 12 months.

While the usefulness of OCs in PCOS patients is well established, the pill should be carefully selected. The appropriate OCs for women with PCOS should contain progestogen which is devoid of androgenic activity or has anti-androgenic properties, i.e., the new generation combined OCs or the pill containing cyproterone acetate (CPA)[20,21]. The patient should be on OCs for long term until the pregnancy is desired, since the discontinuation of treatment results in the recurrence of symptoms in most cases[18].

Surgical treatment of PCOS by wedge resection of the ovaries which was commonly performed in the past is almost outdate at present. Surgical treatment did not eliminate the cause of PCOS. After surgery, the syndrome

reappears in most of the cases. Pelvic adhesion, a sequelae of surgical procedure, is also the great concern in the infertile cases. During recent years, less invasive surgical treatment has been introduced. The small peripheral cysts were cauterized by using electric or laser through laparoscopy[22,23]. The effectiveness of this method remains to be seen in long term follow up.

Since most patients with PCOS are obese, weight reduction by dietary restriction and exercise should be strongly advocated. This measure will lessen hyperinsulinemia and hyperandrogenemia. Some patients have spontaneous ovulation and pregnancy after weight reduction[24].

Conclusion

PCOS is a common disorder of women in reproductive years. The pubertal onset of menstrual disturbances, clinical manifestations of hyperandrogenemia and obesity should alert the physician to look for this disorder. Diagnosis of PCOS usually relies on clinical, biochemical and ultrasonic appearance of the ovary. Once diagnosis has been made, proper management should be given to prevent the late consequences of this disorder. Knowledge about PCOS grows rapidly during the past decade, but many questions remain unanswered. This topic will remain one of the most interesting issue in gynecological endocrinology in the next decade.

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Special Article

The Pathologist and Perinatal Medicine Part II Contributing Directly to Patient Care

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In perinatal medicine the pathologist can make an important direct contribution towards enhancing the overall quality of patient care, not only because of the often urgent need for accurate information for reproductive counselling but also because of the particular nature of grief reactions to fetal and neonatal death. He or she has the opportunity to be part of a clinical team and abolish forever the image, which has persisted until recently in large hospitals and pathology institutes, of a remote and often uncommunicative figure, hunched over a microscope or autopsy table, in search of rare cases to add to his collection. The notion of the pathologist as physician is not a new one and several areas of clinical medicine, such as gastroenterology, hepatology, dermatology, nephrology and medical genetics have now, for more than a decade and to great mutual benefit, incorporated specialist pathologists into their clinical and academic environment ; and the concept of multidisciplinary patient management teams is now widely accepted. The pathologist, through the clinical consultative process of a perinatal autopsy or fetal pathological examination, and by facilitating other aspects of perinatal death management, can make several very positive contributions to direct patient care in perinatal medicine.[1] These contributions include the provision of accurate, timely and sensitively expressed verbal and written information both to clinicians caring for the mother and baby, and where requested and appropriate, directly to the parents and family. Of equal importance is the provision of accurate facts and expert opinion to aid in genetic diagnosis and counselling. Furthermore, it has long been recognised that information derived from an intelligently performed autopsy plays an impotant role in the process of clinical audit at unit and at hospital level, providing confirmation of prenatal and postnatal ultrasound findings on the fetus, placenta and neonate, defining iatrogenic

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complications and evaluating the effectiveness of therapeutic interventions.[2,3,4] Very few special resources other than an interested well informed and motivated pathologist, with good communication skills, supported by a sensitive, equally motivated and clinically aware pathology technician, are needed.[1] It is essentially the quality, timeliness and relevance of the information that defines this contribution to direct perinatal care. As well as providing information of direct clinical relevance, the pathologist can make a substantial contribution to the psychosocial management of fetal and perinatal loss, and this aspect of the pathologist's role will be reviewed in some detail later in this paper.

General Information for Parents

The pathologists first responsibility to parents who have consented to an autopsy on their dead baby or fetus is to provide, generally through the obstetrician or neonatologist directly involved, a clear, accurate, and meaningful preliminary autopsy report, preferably within 72 hours of the autopsy and with sufficient information to allow early discussion with parents. Such a report should include macroscopic findings, with a comment on their likely significance, an indication of further work in progress such as bacteriology, virology or cytogenetics, with, where appropriate, recommendations about further diagnostic tests on maternal blood, and should preferably also include a clear provisional summary linking the clinical and pathological findings as far as possible. It is also helpful if the pathologist can indicate to what extent, in the individual case, histopathological examination is likely to further contribute. For example, while it is clearly essential to await a final histology report before counselling for cystic renal disease, with an isolated neural tube defect, histopathological examination is unlikely to alter the final diagnosis and genetic counselling can therefore often be arranged at an earlier date. If an unusually long delay is expected before either the provisional or the final report is issued in hard copy, then direct discussion with the clinician with an interpretation of the findings, as far as possible, is a professional courtesy usually greatly appreciated. Too often, clinician and thus patients are left waiting for 6-8 weeks with either no report at all or only with uninterpreted and therefore virtually meaningless pathological descriptions.

Bereaved parents have many, often unspoken, questions in their minds such as: *why us? or how did it happen? or did the baby feel pain or suffer? or whose fault was it? or was there anything we did or did not do that caused it?* as well as the more obvious and more easily answered questions about recurrence risks, prevention and earlier detection in subsequent pregnancies. Pathologists can contribute to helping resolve parental guilt, by remembering at the

start of each autopsy that some or all of these questions may need to be addressed.

There is some evidence that, as well as its medical usefulness, a perinatal autopsy can be psychologically helpful for parents by reducing their feelings of guilt. Parents often consent to an autopsy, even when there is already a known clinical explanation for the death.[5] Even if nothing unusual is found, the simple demonstration that the baby is normal can be reassuring. It may therefore be useful to emphasize these benefits to the family, rather than to discuss any unresolved clinical issues, when seeking consent for autopsy. When discussing autopsy, parents should always be informed of what the process means, that organs may be retained for further examination and that they have a right to refuse or limit the procedure.

Often early and sensitive communication, particularly in cases of unexpected intrapartum death, where there may be expressed or suppressed anger or hostility toward the obstetrician, will defuse the situation and avert the threat of litigation.

Perhaps the most difficult task both for pathologist and clinician is to try and explain to parents the sudden intrauterine death, a few weeks before the expected date of delivery, of an apparently normally developing baby of a mother who has had regular antenatal care, who has no obvious risk factors and is anticipating the birth of a healthy infant. There is as yet very little evidence concerning risk factors for sudden, unexplained, late fetal death, and once specific identifiable causes such as massive fetomaternal haemorrhage and overwhelming fetal infection have been excluded, it is perhaps best to simply indicate that, as yet, there is very little known about the reasons why some apparently normal babies die suddenly before the onset of labour and that all that is known about the mechanism is that there is evidence of sudden severe fetal anoxia.

General Information to Clinicians

If the pathologist is to fulfil a role in improving the quality of direct patient care, he or she should be prepared to address a range of clinical questions at the time of autopsy and be prepared to produce evidence in support of his conclusions. These include 1) assessment of agreement between clinically assessed gestational age, pathologically assessed gestational age and fetal growth, 2) timing of death and likely mechanisms and sequence of events leading to death, 3) specific abnormalities in fetus, neonate or placenta contributing to death, 4) factors in antenatal intrapartum and where appropriate neonatal periods contributing to final process of death, 5) existence and significance of other abnormal findings, 6) comparisons with clinical diagnoses and reasons for any discrepancies, 7) any unexplained and unaccountable patho-

logical findings and 8) significance of any of the findings for the family's future reproductive potential and on any living siblings and ensure a mechanism for discussing these issues further. If the pathologist is in the habit of routinely addressing all these questions and ensuring that appropriate tissue is sampled at autopsy to answer the first two questions and that the final summary contains answers to all the questions, then one important clinical function will be fulfilled. The simple process, often overlooked, of assessing organ maturity by pathological markers such as brain convolutions, renal cortical development and structural maturation of the lungs, and correlating these with growth parameters, ultrasound evidence of gestational age and menstrual dates, is a useful habit. Likewise, microscopic examination of the growth plate of a rib, together with qualitative assessment of the amount and pattern of fat in the fetal cortex of the adrenal using a simple fat stain on frozen tissue, and assessment of involutionary, or socalled "stress-induced" changes in the cortex of the fetal or ear lyneonatal thymus, can provide a striking picture which may help distinguish between a fetus who dies suddenly without evidence of obvious pre-existing compromise and a fetus or newborn who has been severely stressed for some time, such as occurs when there is fetal hydrops from any cause, in some chronic fetal infections and to a lesser degree when there is a prolonged growth retarding stress.

Information for Clinical Audit of Individual Cases

Part of the function of a perinatal autopsy is to help provide reassurance to individual clinicians that their diagnoses were accurate and that their interventions were appropriate and free of complications. This depends on a careful and unbiased assessment of the full clinical history with the pathologist being aware of all interventions of clinical diagnoses and of the results of any special investigations. It is therefore up to the clinician to ensure that medical records and other information are readily available to the pathologist and, if not then, to communicate full details in some other way. Clinicians may wish to be present at the autopsy or may wish to be involved with special dissections of organs of interest to them, for example, a paediatric cardiologist or surgeon may wish to see and handle a heart with complex malformations.[7] This is to be encouraged since both may greatly benefit from the discussion, even if it is necessary for the pathologist to reorganise his or her time.

As well as providing accurate and clinically relevant reports in sufficient detail to allow full discussion with the family of the dead baby, the pathologist can contribute actively to clinical audit processes, both internal audit and where it exists, regional perinatal mortality audit, through active participation in perinatal morbidity mortality review

committees or meetings, and in any regional perinatal committee set up to monitor perinatal outcomes. The pathologist's contribution to hospital perinatal mortality meetings needs, however, to be more than the demonstration of a catalogue of unusual pathological findings, which, though undoubtedly fascinating to pathology colleagues, may have little bearing on the clinical problems under scrutiny. Rather than using valuable discussion time to describe pathological findings in tedious detail, the pathologist can more effectively contribute, as a well informed member of the specialist team, by producing evidence to answer key clinical questions about the mechanisms, time course and severity of disease, and by highlighting unexpected complications, and any discrepancies between clinical, ultrasound and pathological findings. It is in the peer review environment of a mortality meeting that errors of clinical judgement may be frankly discussed, and this may result in recommendations to change specific clinical practice. Again, this type of contribution depends, not only on the quality of the autopsy, but is greatly enhanced if the pathologist has a broad overview of current issues and controversies in high risk obstetrics and perinatology. In an ideal situation, the pathologist will arrange to have easy access to current perinatal literature, including overviews of clinical trials, and will keep up an active and informal dialogue with clinical colleagues in order to maintain and update knowledge of the evidence on which modern obstetric practice is now based. In this way, his or her clinical knowledge base is continually updated, and he or she is less likely to make inappropriate diagnoses, comments or recommendations on pathology reports that may later embarrass the clinician, that risk misinterpretation by clinician or patient or, worst of all, encourage litigation. The pathologist must, however, be sufficiently modest and sufficiently realistic to acknowledge the limitations of the perinatal autopsy, and recognise the lack of hard evidence to support many clinical concepts.

Guidelines for perinatal-death review committees and for their annual reports have been developed and can be modified to meet local needs.[8] When there are set standards for perinatal mortality-morbidity review committees and when appropriate items are included in their annual reports, then there is a chance that their recommendations will be taken seriously by colleagues, hospital administrators and those responsible for perinatal care policy.

Specific Information to Enable Identification of Genetic Diseases

Good-quality reproductive counselling after the death of a fetus or neonate, with known or previously unsuspected abnormalities, or after termination of pregnancy for pre-

natally diagnosed abnormality, depends on the accuracy of diagnosis.[9] The accuracy of diagnosis is often greatly enhanced, particularly where there are multiple congenital abnormalities, not only by the quality of pathological examination of the baby and the placenta, but also by the breadth of the pathologist's background knowledge in medical genetics and clinical dysmorphology, and by the level of co-operation between pathologist and medical geneticist/ clinical dysmorphologist. Apart from the cost of karyotyping, which should only be done with clear indication, no special or expensive material resources are needed, as the quality of information is largely determined by knowledge, expertise and good communication. The pathologist and the medical geneticist can usually, with the help for difficult cases of one of the computerised databanks,[10] make a genetic diagnosis adequate to allow recurrence risk counselling, help future management planning and where available, propose prevention strategies. Information derived from pathological examination may be helpful in virtually all the areas usually covered during a genetic counselling session, i.e., diagnosis, natural history, recurrence risk,. therapies and future planning. It is clearly important that an autosomal recessive dysmorphic syndrome, such as Meckel-Gruber syndrome, Fraser syndrome or Smith-Lemli-Opitz Type II syndrome, be distinguished from those sporadic and chromosomal syndromes, which they may externally resemble, and that those sporadic conditions, currently considered as either developmental field defects or vascular disruptions, for example, amniotic band syndrome, schisis association, VACTERL sequence or caudal regression sequence, be distinguished from both of the above.

Specific Information to Enable Identifcation of Nongenetic Diseases

By recognising the variable manifestations in the fetus and placenta of nongenetic maternal diseases, for example, systemic lupus erythematosis, antiphospholipid antibody syndrome or unsuspected maternal diabetes, the pathologist can make a valuable contribution to diagnosis and future management planning. Moreover, if the pathologist is aware of the variable presentations of chronic intrauterine infections affecting the fetus, such as toxoplasmosis, cytomegalovirus, parvovirus, varicella-zoster or syphilis, he or she can recommend additional tests on maternal or fetal blood. If these diagnoses are able to be formally confirmed after autopsy when, as is often the case, there is no single, pathognomonic feature, the overall diagnosis may be as accurate as possible, and the risk of recurrence in a subsequent pregnancy may be assessed.

Psychosocial Management of Perinatal and Fetal Loss

There is now considerable interest worldwide in the psychopathological and psychotherapeutic aspects of fetal and neonatal bereavement and in variations in the length and intensity of grief reactions in specific situations.[5,11-18] While there is an overall pattern of normal and pathological behaviour after perinatal loss, some differences have been identified. Reactions to deaths of very low-birthweight babies, after neonatal intensive care,[19] may differ from those following unexplained late fetal death, and these may again differ from reactions to spontaneous second trimester fetal loss, first and second trimester social terminations or genetic terminations[14] and after death of one of a pair of twins or of higher orders of multiple pregnancy, including fetal reduction procedures.[20] Responses to second trimester loss have recently been identified as being unexpectedly intense.[17,18] Cultural, educational, religious and socioeconomic factors,[5] as well as partner support and parental immaturity,[16] have all been proposed as influencing grief reactions. Other than a small amount of information on the established Asian immigrant groups in Britain,[21] there is very little published work on attitudes to fetal and perinatal death outside a European and North American context, and further work on this subject may be of value in the Asia-Oceania region. Despite the interest in the subject of perinatal bereavement in general, there have been very few systematic evaluations of the value of support and counselling[15] and only one randomised controlled trial.[22] In hospitals where this type of support is not yet routinely offered, there may be a place for further trials of the effectiveness of various methods of supportive management.

There is a very significant role for the pathologist and pathology technician in the psychosocial management of fetal and neonatal loss, much of which revolves around the process of helping the patient confirm the reality of fetal or neonatal death,[11] and includes having helpful information available early, encouraging naming the baby, making the funeral arrangements, arranging the location of a marked grave and the collection of mementoes and other artefacts.[5] Most aspects of this process can be encouraged, actively supported or facilitated by the pathology service. There is some evidence[5,23] that grieving is facilitated if the mothers and other family members are permitted to hold the baby, however small and malformed, for as long as they wish, within reasonable practical limits, after death. It has been suggested that maternal perceptions of fetal abnormality are exaggerated if the mother is not allowed to see and hold her congenitally malformed fetus, and that many expect it to look much worse than it does.[13] Either research needs ok pathology department convenience must not be allowed to override parents rights to handle their

baby.

In exceptional cases such as when the confirmation of a suspected rare and inherited metabolic disorder requires autopsy within two hours of death, in order to collect fresh tissues for biochemical analysis, this should be fully discussed with the family and with the pathologist before delivery, or before withdrawal of life support. The pathologist must then be prepared to carry out an urgent autopsy, if necessary, in the middle of the night. Fortunately, such events are rare but require careful co-ordination so that valuable genetic information, essential for counselling the family, is not lost.

As it is not uncommon for family members to wish to view the body again after autopsy, it is desirable that the pathologist and technicians develop methods of cosmetically satisfactory reconstruction of the baby. Small fetuses are difficult to reconstruct, as the skin is usually too thin to hold even fine sutures, and alternative techniques have been used, including the use of a colourless cyanoacrylate adhesive ("superglue").[24] Normally the face, hands, feet and genitalia are never incised but are left untouched, and it is rare that limbs need to be examined. If, however, as is essential, a fetus or neonate is suspected of having skeletal dysplasias, long bones have to be removed for histopathological examination to aid classification and genetic counselling. Then reconstruction of limbs with wooden rods or rolls of stiff thin cardboard to restore rigidity is essential. Skin defects in the small fetus that cannot easily be repaired can be closed with a patch of amnion and cyanoacrylate glue.[24]

Requests to dress the baby after autopsy, often in clothes bought specifically for the purpose, should be respected by the pathologist, as should any requests to include accompanying toys, flowers, photographs or other objects for burial with the body. A pathologist who, from carelessness, haste or insensitivity overlooks these ritual aspects of perinatal death can cause considerable additional distress. Similarly, it is occasionally necessary for the pathologist and technical staff to allow simple religious ceremonies to take place in the mortuary for an infant of fetus who is not having formal funeral rites.

Photographs of the dead baby may be an important aid to coping with the realities of perinatal death.[11] The polaroid type of photos, often taken in the delivery room, while adequate in the short term, fade and discolour, and thus permanent colour print photographs or slides of the baby or fetus, both wrapped and unwrapped, are preferable. It has been suggested[13] that photos of the unwrapped, naked fetus or newborn are particularly important in helping the mother to cope with the reality of the death. For the same reason, however, the baby should not be made to look too artificial and doll-like. It is of course possible for delivery room staff to perform all these functions, and this may be necessary if there is to be no

autopsy. It is, however, our practice to receive all dead fetuses and neonates into the hospital mortuary so that the pathology technical staff can collect mementoes and take suitable photographs for the parents. In the busy environment of a teaching hospital delivery suite, there may not be time to take quality photographs there, whereas in the pathology department, there are less competing pressures. It hardly needs to be emphasised[13] that the usual type of photographs taken for pathology records are usually not suitable for parents as mementoes.

The provision of a small package of mementoes of the dead baby or fetus is now becoming a standard part of perinatal autopsy practice, and should be carried out even if there is no autopsy. Nursing staff in neonatal intensive care units have done this for some years, but it is only more recently that the practice has extended to genetically terminated second-trimester fetuses and to stillborn babies. Rates of acceptance of such mementoes are high.[25] Such mementoes may include footprints and handprints made with an inkpad onto a small card bearing the baby's name, hospital identification bracelets and locks of hair. These, together with colour or black-and-white print photographs, are collected as a small package, as a routine on every baby and fetus, and offered to the mother at the time of postnatal follow-up visit or subsequent counselling.

Naming the baby or fetus is usually encouraged and once this is done it is appropriate that the pathologist include the given name of the baby or fetus on any reports and correspondence. Mistakes by nursing or medical staff in identifying the sex of the fetus, most common in second trimester deaths, can be a cause of considerable parental distress. Nursing and medical staff in the delivery suite who are uncertain of the gender of smaller fetuses are advised to leave this aspect of the clinical examination to the pathologist, who can confirm external impressions by internal examination. The hypertrophic clitoris of the second trimester female fetus is the usual reason for confusion; a fetus may be incorrectly designated as a boy, with the parents later being told that the documented gender has been changed, and they may then feel obliged to change the baby's name. For larger neonates with ambiguous genitalia, the pathologist is strongly advised to consult the paediatrician to find out the parents perception of gender in order to avoid tactless and potentially distressing errors in the written report.

An additional area in which the pathologist can play a useful role in patient care and which has been standard practice in our hospital for at least six years, is the production, for the parents request, of a summary of the autopsy report in nonmedical language. Although the value of these reports has not yet been critically evaluated, they appear to be helpful and are widely requested. They are not sent directly to the mother but

sent through a medical officer nominated by her, which may be her general practitioner, her obstetrician or her paediatrician, so that the content and style can be scrutinised for appropriateness, as well as for her level of education and general understanding, modified if needed, or passed on directly with further explanation and discussion. In the six years since we instituted this practice, we have not yet had any clinician request a modification to any plain language report. It is not our usual practice to offer the full technical report to parents, and though this is never withheld if requested, we always strongly recommend that it be fully explained by the pathologist or clinician at the time of handing it over.

The most obvious and direct role that the pathologist, as a professional, can play is when he or she becomes directly involved in the postautopsy counselling, as has been the practice in some centres for many years.[26] In reality, this is rarely practical for busy pathologists with a large and urgent surgical pathology workload, and impossible in regions where there is a serious shortage of pathologists.

The pathologist may, however, choose to have professional input in an advisory capacity into groups such as SANDS (Stillbirth and Neonatal Death Society) which provide support for self-help networks of bereaved parents, or by various other means, make himself or herself available to parents and to the community for general advice. Some general caution in this area is however advised. A recent annotation which summarises contemporary attitudes to the management of perinatal death highlights the emerging problem, in Europe, North America and Australia, of magnifying every first-trimester miscarriage into a major reproductive catastrophe.[27]

Unless there are strong religious objections, then autopsy consent for a fetus (if required by law) or for a neonate is usually easy to obtain, so long as an adequate explanation of the benefits and of the process itself are given. While it is the responsibility of the medical staff to seek consent, this may be easier to discuss when the clinician knows that the autopsy is to be carried out by an experienced perinatal pathologist and, therefore, more likely to yield meaningful results. It may also be worth emphasising that an autopsy is not a complex laboratory test but essentially a clinical examination and consultation. All clinical staff concerned should be aware, however, that there are limitations to the amount of information obtainable from autopsy, particularly with macerated babies and should try not to raise unrealistic hopes and expectations in the parents.

Midwives and perinatal nurses can contribute a great deal, if they are themselves well informed about the process of autopsy and its value and can do much to help the patient come to a decision. This is an area which

can be usefully included in post-graduate perinatal nursing courses. Pathologists can do much to educate nursing and other clinical staff not only about the reasons for and benefits of autopsy examination, but also about the existence of available options and the additional services available to support management of the grieving process and, thereby, help dispel fears and, outdated, or negative attitudes.

In those countries where a fetus or newborn under 28 weeks gestation does not require a death certificate or need to be legally disposed of, it is often of help to the parents to know that an acceptable form of disposal will, nevertheless, occur. This can include cremation in the hospital with scattering of ashes in a specified place, such as a small memorial garden specified and dedicated to the purpose, or burial in a specified but unmarked grave. In Australia, where birth registration death certification and burial or cremation is mandatory for all fetuses and neonates over 20 weeks gestation or 400 grams birth weight, there is an increasing trend for parents to request simple funerals with burial or cremation of these unregistered smal-ler fetuses. This is particularly so, after genetic terminations of pregnancy, where the decision may have been a difficult one and the pregnancy much wanted. It is probably not advisable for parents to be told that a fetus has been cremated or buried, if in reality it has merely been discarded along with usual pathological waste. Clearly, however, theimportance attached to these issues depends on community, religious and cultural practices and on the attitude of the parents towards the particular pregnancy.

In addition to recognising cultural differences in attitudes to perinatal death, the pathologist needs to be aware of the various cultural attitudes relating to the placenta and its handling and disposal, ranging from general disgust to a rich mythology surrounding its overall significance.[28] After necessary tissue samples have been taken, cultural attitudes should be respected and accommodated, as far as is reasonably practical, unless there is an overriding medical reason or a major infectious hazard.

Limited Autopsy

When there is a reluctance by parents to consent to full autopsy, then some form of limited procedure may be acceptable and can often provide reasonable quality information for reproductive counselling. The pathologist should not discourage this approach but regard it as a creative challenge. In some communities where there is strong local prejudice against autopsy, it may be necessary for the pathologist to develop alternative approaches. These may range from needle biopsy of major organs under ultrasound guidance[29] to ingenious techniques requiring considerable pa-

tience and manual dexterity, whereby abdominal and thoracic organs are removed for examination through a limited epigastric incision. Postmortem ultrasound scans are occasionally useful as an alternative or an adjunct to autopsy, as is contrast radiography. Clearly, some of these techniques are costly and others time consuming, and this needs to be balanced against potential benefits to the parents and clinical staff, as well as against the quality of information gained and its contribution to audit and to epidemiology. It is up to the pathologist, nevertheless, to inform clinicians of all available alternative techniques, rather than take an 'all or none' approach to an autopsy. Much valuable information can be gathered simply by careful external examination, and detailed documentation, with clinical photography and a range of anthropometric measurements[30] and plain radiographs.[31]

Regardless of whether or not there is consent for autopsy, efforts should be made to ensure that the placenta is made available to the pathologist and submitted unfixed, so that it can be used for cytogenetics or microbiological investigations, as indicated. Even if autopsy consent is withheld, examination of the placenta by an appropriately experienced pathologist, with a full understanding of the clinical issues, may be able to confirm important diagnoses contributing to perinatal death, or to fetal malformations. Obvious examples include diagnosing amniotic fluid infection as a cause of preterm birth or neonatal infection, identifying significant vascular pathology seen in lupus and hypertensive disorders in spiral arteries on the maternal surface of the placenta, identifying amniotic bands and identifying severe villitis of chronic fetal infection or the characteristic inclusions of human parvovirus infection. Conversely, examination of the placenta by a pathologist can provide useful negative information, which may not be obvious on general inspection by obstetrician or a midwife, who may an label as "unhealthy looking" or "infarcted", a term placenta which on pathological examination proves to show only calcification and/or intervillous fibrin, both essentially of no significance. There is an increasing trend to try and attribute perinatal death or adverse perinatal outcome to placental lesions,[32] not always on good evidence. This is being driven by the threat of litigation, most commonly when cerebral palsy develops after alleged birth asphyxia and where, to protect the obstetrician, there is a need to search for placental evidence of antepartum fetal injury or disease. It is up to the pathologist to make a careful and dispassionate assessment and to avoid overinterpreting trivial lesions as evidence of prenatal injury. It is important, therefore, that placental examination, particularly if there is no autopsy, or if the baby survives but is neurologically compromised, be carried out by an appropriately experienced pathologist and not merely

sent to a busy general surgical pathology department, fixed in formalin, with no clinical information and with only a polite but cursory request for "histopathology please".

Multidisciplinary Management of Prenatally Diagnosed Fetal Abnormality

In the last few years multidisciplinary teams for the management of prenatally diagnosed fetal abnormalities have become accepted practice in many centres including our own, which started as early as 1987.[33] Such a team, often called a dysmorphology group, fetal board or antenatal diagnosis and counselling service, are probably most effectively run as prospective diagnosis and management groups, enabling the concentrating of clinical material and the expertise of relevant specialists to co-ordinate the management of referred cases.[33,34] Groups such as these tend to meet regularly, often weekly, if the volume of referred material should warrant this, and by means of team discussion, review and discuss the abnormal ultrasound scans, arrange initial counselling, recommend further action such as additional scans or invasive procedures, review results again and recommend options for management, which may include proceeding with the pregnancy, with a planned delivery at or before term, offering fetal therapy where available or offering termination of pregnancy. patient and her partner are seen by an appropriate medical member of the group, and the diagnosis, its implications and the various management options are presented, with non directive counselling. Initial counselling is often undertaken by a perinatologist, particularly for common and well understood conditions, by a medical geneticist for rare inherited disorders and dysmorphic syndromes, by a paediatric cardiologist for congenital heart disease or by a paediatric surgeon for potentially treatable conditions such as bladder outlet obstruction. During the days or weeks between diagnosis and decision making, a nurse counsellor is available to support the parents and facilitate contact with the appropriate group member; once a decision is made, this person can then provide ongoing support for that decision. Cases are seen on referral, and the referring clinician is kept fully informed. It is important that such a group does not degenerate into an exclusive club for collecting exotic cases for publication, and that it remains primarily a patient care service. However, it is desirable that the group's performance be internally evaluated from time to time and that any diagnostic or clinical management algorithms or protocols be regularly and critically reviewed against current evidence-based best practice. Such groups, which seem to be most effective if they remain small, usually include, as core members, those senior medical staff with expertise in fetal ultrasound, maternal-fetal medicine, neonatal paediatrics, paedi-

atric, and where available, fetal surgery, medical genetics and perinatal pathology. While access to expertise in perinatal microbiology and haematology, and in paediatric clinical chemistry, is desirable, most clinical problems present as a result of secondtrimester scans, and most can be managed by the core group. In order to fully contribute to patient management of prenatally diagnosed fetal abnormality, the pathologist must perceive him self or herself to be a fully committed team member and earn this place by demonstrating the same level of awareness of current literature, of enthusiasm and of sensitivity as the clinicians. The regular presence of a pathologist in this type of forum is beneficial in several ways: 1) The pathologist, together with the medical geneticist, often has the best grasp of likely differential diagnoses of multiple abnormalities presenting on scan and can advise on specific areas of the fetus to be assessed in subsequent detailed scans. 2) A perinatal pathologist with some clinical pathology experience is in a position to advise or at least co-ordinate investigations on amniotic fluid or on fetal blood samples collected by cordo-centesis. 3) Should termination of pregnancy be the agreed management decision, then the pathologist is alerted early to the need for complex or specialised autopsy procedures, urgent biochemical tests on fresh tissue or any specialised imaging procedures, as well as any special social religious or cultural needs of the parents.

If the pregnancy is terminated after prenatal diagnosis, the pathologist has specific responsibilities when examining the fetus, and these have been summarised as threefold.[35] The primary objective is the confirmation of the abnormality for which the pregnancy termination was performed. The second is the careful examination of fetus, placenta cord and membranes for any abnormality or complication related to or arising out of a prenatal diagnostic or therapeutic intervention. The third is the meticulous documentation of all abnormalities present, in order to allow accurate genetic and general diagnosis and counselling. The first two represent part of the pathologist's quality control function in prenatal diagnosis by ultrasound and, the effectiveness of this process has been confirmed.[36,37] The last represents one of the pathologist's direct contributions to clinical care.

It could be said that the commitment by a pathologist to this type of multidisciplinary group management exemplifies all the roles that the pathologist can play in perinatal medicine, that is in direct patient care, in the auditing of prenatal diagnostic procedures, in the monitoring of outcomes of high technology intervention and in the improvement of epidemiological data through more accurate diagnosis of fetal abnormality.[38]

Conclusion

It should be emphasised that if

the pathologist is able to see each patient not as an unusually large and interesting pathology specimen but in the same way, the clinician, as a complete fetomaternal dyad in a broad biological and sociodemographic context, then his or her contribution to patient care is immeasurably enhanced. Thoughtful examination of the deceased neonate or fetus and its placenta by a motivated and well-informed pathologist can contribute much to direct patient care. It is important, however, that this service is accompanied by careful and culturally sensitive handling of the body, and by timely and sensitive communication with clinicians and where requested, parents, both before and after the autopsy.

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