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OBSTETRICS

The Prevalence of Antiphospholipid Antibodies in Severe Preeclamptic and Normotensive-Term Pregnant Women

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ABSTRACT

Objective To determine the prevalence of antiphospholipid antibodies in severe preeclamptic and normotensive-term pregnant women.

Design Cross-sectional study.

Setting Department of Obstetrics and Gynaecology, Siriraj Hospital, Mahidol University.

Subjects Sixty women with severe preeclampsia and one hundred and twenty normotensive-term pregnant women.

Methods Blood samples were obtained from sixty severe preeclamptic women and one hundred and twenty normotensive-term pregnant women. All samples were analyzed for lupus anticoagulant by kaolin clotting time and for anticardiolipin antibodies by ELISA. The clinical course of all women and perinatal outcome were recorded.

Results Positive antiphospholipid antibodies were detected in eight (13%) out of sixty severe preeclamptic women and one (0.8%) out of one hundred and twenty normotensive-term pregnant women. Five of eight infants of antiphospholipid antibodies positive-severe preeclamptic women were small for gestational age. This was a significantly larger proportion than that of antiphospholipid antibodies negative-severe preeclamptic women (10/52) ($P = 0.018$).

Conclusion The prevalence of antiphospholipid antibodies in severe preeclamptic women and in normotensive-term pregnant women in this study is comparable with the previous studies. Positive levels of antiphospholipid antibodies in severe preeclamptic women increase the risk for fetal intrauterine growth retardation.

Key words : severe preeclampsia, antiphospholipid antibodies, small for gestational age

Preeclampsia, a common complication of obstetrics, is the major cause of maternal mortality throughout the world. Antiphospholipid syndrome is one of the autoimmune diseases, however it may be found in normal person.[1,2] Interest in this entity by obstetricians have resulted from the association between the antiphospholipid antibodies (aPL) and pregnancy complications such as arterial and venous thrombosis, spontaneous abortion, intrauterine growth retardation and intrauterine fetal death.[2,3] There are now evidences that some treatments can improve these pregnancy outcomes.[2-9]

Although many reports showed the association of antiphospholipid antibodies (aPL) with preeclampsia,[10-12] some did not.[13] Because of the controversy, we want to find the prevalence of aPL in severe preeclamptic and normotensive-term Thai pregnant women.

Materials and Methods

From January 1, 1992 to October 31, 1994, blood samples were obtained from severe preeclamptic and normotensive-term pregnant women admitted in the Obstetrics and Gynaecology Department, Siriraj Hospital. Informed consent were obtained. None of the subjects were administered the following drugs : steroid, aspirin, heparin, chlorpromazine, procainamide, hydralazine, phenytoin, quinidine and antibiotics.

Twelve ml of blood were obtained by venipuncture and placed into two tubes. The first 15 x 120 mm-centrifuged tube containing 9 ml of blood mixed in 1 ml of 3.8% sodium citrate solution. The remaining was placed in an empty tube (13 x 100 mm in size). Each tube was labeled the patient's name and her hospital number. The former was analyzed for lupus anticoagulant by kaolin clotting time (KCT), the method of Exner et al.[14] The latter was analyzed for IgG anticardiolipin antibodies (ACA) by ELISA, the method of Loizou et al.[15]

The results were reported in seconds for KCT and optical absorbance (OA) for IgG ACA, valued above 100.2 seconds and above 0.230 OA were considered significant.[16,17] Clinical data on the patients and infants were recorded. The groups were compared regarding clinical data, gestational age, fetal birthweight, and APGAR score. The means of data were compared using an unpaired-t-test. The number of positive test for aPL were compared using Fisher's Exact test. The difference were considered to be significant for P-value < 0.05.

Results

During the study period there were 60 severe preeclamptic and 120 normotensive-term pregnant women. The characteristics of all subjects in this study, including age, gestational age, fetal birthweight, and APGAR score, are presented in Table 1. The mean of fetal birthweight was 2,387.5 ± 608.0 g in the study group, and 3,056.5 ± 345.9 g in the control group. The number and prevalence of positive test for antiphospholipid antibodies in both groups are shown in Table 2. The prevalence was 13% in the study group and 0.8% in the control group. Table 3 shows the gestational age, fetal birthweight, and APGAR score of the positive test. Of the eight women with severe preeclampsia, five (62.5%) had infants who were small for gestational age (SGA).

Among severe preeclamptic group, the fetal birthweight of positive group was significantly lower than that of the negative group, the percentage of SGA was significantly higher in the positive group (Table 4).

Table 1. Maternal and neonatal data of the two groups

	Severe preeclampsia		Normotensive	
	Mean	SD	Mean	SD
Age (years)	26.13	5.78	25.33	4.76
Gestational age (weeks)	36.83	2.44	39.27	1.38
Fetal birthweight (grams)	2,387.5	608.0	3,056.5	345.9
APGAR score at 1st minute	7.1	2.5	9.3	1.3
APGAR score at 5th minute	9.0	2.2	9.8	0.4

Table 2. Number and prevalence of positive antiphospholipid antibodies for the two groups

	Severe preeclampsia	Normotensive
Positive KCT	5	0
Positive ACA	3	1
Positive aPL	8	1
Prevalence of aPL (%)	13	0.8

Table 3. The positive aPL data

Case No.	Gestational age (weeks)	Fetal birthweight (grams)	APGAR score (at 1st, 5th min.)	KCT (seconds)	ACA (OA)
1	38	2,450*	9, 9	111.3	0.030
2	40	1,970*	1, 5	145.5	0.105
3	35	1,850	6, 9	145.0	0.028
4	36	1,800*	7, 10	112.6	0.057
5	37	2,500	9, 10	> 180.0	0.026
6	36	1,520*	7, 9	80.7	0.258
7	34	1,450*	5, 10	67.0	0.831
8	30	1,300	9, 10	60.6	0.570
9	40	3,500	10, 10	75.0	0.244

* Small for gestational age

Table 4. Comparison of gestational age, fetal birthweight, percentage of SGA and APGAR score at 1st, 5th min. in the severe preeclamptic women

	Severe preeclampsia				P-value
	Positive aPL		Negative aPL		
	Mean	SD	Mean	SD	
Gestational age (weeks)	35.75	2.96	37.0	2.34	0.179*
Fetal birthweight (grams)	1886.25	496.09	2464.61	590.0	0.001*
SGA infant (%)	62.5		19.2		0.018**
APGAR score at 1st min.	6.5	2.6	7.2	2.6	0.469*
APGAR score at 5th min.	9.0	1.7	9.0	2.3	0.964*

*Unpaired-t-test

**Fisher's Exact test

Discussion

Our study has shown that the positive aPL were detected in eight (13%) out of 60 severe preeclamptic women and one (0.8%) out of 120 normotensive-term pregnant women. These prevalence are comparable with the previous studies.[10-12] Branch et al reported that 16% of severe preeclamptic women had significant levels of aPL, whereas none in normotensive controls of similar gestational age.[12] Taylor and Skerrow, however, found no significant difference in the prevalence of positive ACA between severe preeclamptic women and normal subjects.[13] The varied results shown by different studies could be due to differences in exclusion and inclusion criteria used for recruitment of patients, different methods of analyzing aPL and varied races.[10,18] We used both KCT and ACA to increase the sensitivity of aPL detection. Several reports found both lupus anticoagulant (LAC) and anticardiolipin antibodies (ACA) in many cases. Pattison et al found that 18% had both LAC an ACA, where as 91% was reported by Rao and Ananthakrisana.[19,20]

As in agreement with several reports, we found that the positive aPL severe preeclamptic women have more SGA than the negative aPL ones, that is 62.5% and 19.2% respectively. Although Branch et al study[12] suggested a significant proportion of early onset severe preeclamptic women had positive aPL, ours did not.

Although there is no complication in a positive aPL normotensive term pregnant women in this study, it is inconclusive. Many complications of positive aPL women, such as arterial and venous thrombosis, pulmonary postpartum syndrome, cerebral infarct, transient monocular blindness, and amnesia, have been reported in several studies.[1,3,10-12] In this study, we found neither eclampsia nor any complications in positive aPL but found six eclamptic women in negative aPL group. We would suggest that in patients at risk of developing preeclampsia screening for aPL should be performed, and close observation for complication should be done in all

positive aPL women. Several reports have shown that treatment with steroid, aspirin, heparin, immunoglobulin, and plasmapheresis can improve pregnancy outcome.[2-9] Further study should be carried out particularly in treatment and methods for analyzing aPL.

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OBSTETRICS

The Amniotic Fluid Index in Normal Pregnant Women

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ABSTRACT

Objective To evaluate the values of amniotic fluid index (AFI) by weeks of gestation.

Design Cross-sectional descriptive study.

Setting Department of Obstetrics and Gynaecology, Maharaj Nakorn Chiang Mai Hospital, Faculty of Medicine, Chiang Mai University.

Subjects and methods Normal pregnant women between 16 and 40 weeks of gestation, had first antenatal visit during first trimester of pregnancy at Maharaj Nakorn Chiang Mai Hospital, between 1st July 1994 and 31st October 1995. All pregnancies were singleton with accurate gestational age. Pregnancies complicated with obstetric, surgical or medical conditions were excluded. The amniotic fluid index was measured by dividing uterus into four equal parts and then measuring amniotic fluid depth of each part vertically by using transabdominal sonography.

Main outcome measures Mean, standard deviation, minimum and maximum values of amniotic fluid index.

Results Total of 830 transabdominal sonographic measurements for the amniotic fluid index were performed. The mean ± standard deviation in centimetres were 10.9 ± 2.2 (7.7-16.0) at 16 weeks' gestation and increased progressively to 16.1 ± 3.7 (8.6-25.7) at 25 weeks' gestation. Then the AFI gradually declined to 11.2 ± 3.3 (6.0-20.0) at 40 weeks' gestation.

Conclusion The mean, standard deviation, minimum and maximum of AFI at each gestational age of normal pregnancies were determined. This data might be useful as a reference standard for AFI in Thai pregnant population.

Key words : amniotic fluid, index

Amniotic fluid volume is an important indicator of fetal well-being. Abnormalities of amniotic fluid volume are associated with poor pregnancy outcome.[1,2] The actual amount of amniotic fluid has been measured using the dye dilution technique.[3,4] But this invasive method,

which involves amniocentesis, is of limited clinical usefulness. With the advent of ultrasonography, a safe and noninvasive technique, has given rise to both subjective and semiquantitative methods of amniotic fluid estimation. The current sonographic technique are indirect measures and only provide estimates of amniotic fluid volume. There is a correlation between abnormal amniotic fluid volume and adverse fetal outcome,[1,2,5] but the reliability of subjective scales are depended on the operators. Phelan et al[6] described a four-quadrant technique, termed as the amniotic fluid index (AFI), for assessing the amniotic fluid volume. However, there is no report using this technique to describe the amniotic fluid index changes throughout pregnancy in Thai population.

This study was conducted to establish the normal range of the amniotic fluid index values by weeks of gestation in Thai pregnant population.

Materials and Methods

Individual AFI measurements were taken in normal pregnant women prospectively in Maharaj Nakorn Chiangmai Hospital, Chiang Mai University, during 1st July 1994 and 31st October 1995. The inclusion criteria were : normal singleton pregnancy between 16 and 40 weeks, reliable dates, early pelvic examination consistent with dates, no ultrasonographic abnormalities. Patients with twin gestation, ruptured membranes, fetal anomalies, suspected fetal growth disorders, abnormal neonatal outcome, maternal diseases were excluded from this study. The study was cross-sectional, only a single examination from each pregnancy was included.

Real-time ultrasound examinations were performed with an Aloka SSD-680 using a 3.5-MHz convex array transducer. With the patient in the supine position, the uterus was divided into four quadrants at all gestational ages (including 16-40 weeks). The linea nigra was used to divide the uterus into right and left, and the midpoint between the fundus and the symphysis pubis divided the uterus into superior and inferior portions. The transducer was placed on the patient's abdomen along the longitudinal axis and perpendicular to the floor. The sum of the maximum vertical pocket measured in each of the four quadrants was given in centimetres as the amniotic fluid index.

The data were stratified into gestational weeks and analyzed by microcomputer statistical programme. The mean amniotic fluid index and the minimum and maximum were calculated for each week of pregnancy.

Results

Eight hundred and thirty individual AFI measurements in normal pregnancy with certain date were taken from 16 to 40 weeks of gestation. The mean age of the pregnant women was 26.36 ± 4.59 (16-36) years. Among these pregnant women 47.7% were primigravida. The mean of the AFI values of all gestational age was 13.0 ± 10.5 cm. (range 5.0-25.7) The results were stratified by weeks of gestation and presented with the minimum, mean and maximum values (Table 1). From 16 to 25 weeks the AFI rose progressively from a mean of 11.1 ± 2.2 cm (range 7.7-16.0) to a maximum mean of 16.1 ± 3.7 cm. (range 8.6-25.7). The index then gradually declined to a mean of 11.2 ± 3.3 cm (range 6.0-20.0) at 40 weeks of gestation.

Discussion

Previous study using the dye dilution technique demonstrated a progressive rise in the amniotic fluid volume during pregnancy until the early third trimester, after that the amniotic fluid volume remained stable and then gradually

Table 1. Amniotic Fluid Index Value in Normal Pregnancy

Amniotic Fluid Index values (cm)					No. of Subjects
Weeks	Minimum	Mean	Maximum	Standard Deviation	
16	7.7	11.1	16.0	2.2	30
17	7.3	11.0	18.1	2.5	32
18	6.5	11.7	17.5	2.8	31
19	8.1	13.4	21.3	3.0	32
20	8.2	13.4	20.3	2.9	33
21	7.8	13.9	18.7	2.8	34
22	7.7	14.1	23.3	3.8	31
23	8.6	14.3	22.2	3.2	30
24	9.2	14.4	23.5	3.1	32
25	8.6	16.1	25.7	3.7	34
26	8.5	14.7	23.4	3.2	32
27	9.7	15.2	21.1	2.9	32
28	10.0	14.4	20.8	3.0	34
29	7.0	14.2	22.8	4.2	36
30	5.0	13.2	23.8	4.3	37
31	7.6	13.5	20.3	3.5	32
32	6.2	13.6	19.2	3.1	31
33	6.8	13.5	20.9	3.6	31
34	6.5	13.1	21.1	3.8	31
35	6.6	13.0	18.2	3.7	31
36	6.3	12.4	21.9	3.4	31
37	5.1	12.1	20.1	4.2	36
38	5.4	11.6	19.9	3.1	38
39	5.4	11.9	20.2	3.4	39
40	6.0	11.2	20.0	3.3	40

decreased until the postdate period.[3,4] The amniotic fluid index provided a semiquantitative analysis of amniotic fluid volume. The technique is simple to perform, safe, reproducible, and reliable. From the previous study, Gadd[7] found that the AFI values were paralleled to the values obtained by the dye dilution technique. As reported by Rutherford et al,[8] 92% of the values of the intraobserver variations from the mean were less than 2.0 cm, and 96% of the values of the interobserver variations from the mean were less than 4.0 cm. The efficacy of the AFI for predicting fetal morbidity and perinatal outcome has been proven by Chamberlain et al.[1,2] Rutherford et al[9] found an inverse relationship between the AFI and the occurrence of a nonreactive nonstress test, fetal heart rate decelerations, meconium-stained amniotic fluid, caesarean

section for fetal distress and low Apgar scores.

This prospective evaluation of the amniotic fluid index in normal pregnancy from 16 to 40 weeks showed the rising of the AFI from a mean of 11.1 ± 2.2 cm (range 7.7-16.0) at 16 weeks to a maximum mean of 16.1 ± 3.7 cm (range 8.6-25.7) at 25 weeks. Then the AFI gradually declined to a mean of 11.2 ± 3.3 cm (range 6.0-20.0) at 40 weeks. Phelan et al[10] and Jeng et al[11] found the same rise in the AFI up to 26 weeks followed by a plateau between 27 and 38 weeks and a gradual decline after 38 weeks. Gadd[7] showed a progressive rise of AFI until 30 weeks of gestation. Moore and Cayle[12] found an increase in the AFI from 12.1 cm at 16 weeks to 14.7 cm at 26 weeks and then progressively declined to 11.0 cm at 42 weeks of gestation. Hallak et al[13] showed a rise from a median of 10.3 cm at 15 weeks to 14.0 cm at 30 weeks of gestation, then the AFI gradually declined to a median of 9.1 cm at 40 weeks.

Phelan et al[6] used an AFI of 5.0 cm as the lower limit of normal and 20.0 cm as the upper limit. Jeng et al[11] defined the normal range as 8.0-24.0 cm, Moore and Cayle[12] and Hallak et al[13] designated the 5th and 95th percentiles for each gestational week as the limits of normal values.

Since we recruited only normal pregnancy into our study of AFI measurement, so we designated the minimum and the maximum values for each gestational week as the limits of normal values. The minimum and maximum values for our total study group from 16 to 40 weeks of gestation were 5.0 to 25.7 cm. Our study determined the normal amniotic fluid index for each gestational age and defined the upper and lower limits of normal values. These values might be useful in clinical practice in evaluating amniotic fluid volume during pregnancy.

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OBSTETRICS

Safety and Tolerance of Zidovudine Treatment in Late Pregnancy among HIV-1 Infected Parturients in Ramathibodi Hospital

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ABSTRACT

Objective To evaluate safety and tolerance of asymptomatic HIV-1 positive parturients who treated with zidovudine in late pregnancy.

Design Prospective descriptive study.

Setting Department of Obstetrics and Gynaecology and Department of Paediatrics, Faculty of Medicine, Ramathibodi hospital, Mahidol University.

Subjects Thirty-five cases of HIV-1 positive pregnant women who attended antenatal care between January 1995 and June 1996.

Results The mean age of study group was 25.8 ± 4.6 years. Most of them were primigravida and lived in Bangkok. The mean duration of zidovudine intake was 24.6 ± 9.5 days with complete treatment 91.4%. Only 20% of them had side effects and most common was nausea and vomiting. The mean birthweight of newborns was 3,004.0 ± 297.4 grams and no asphyxia was observed. Most of them were delivered by normal delivery. No adverse effect and postpartum morbidity were demonstrated. No HIV-1 genome which was performed by PCR technique was detected in peripheral blood of newborns.

Conclusion Zidovudine treatment in late pregnancy is safe and tolerant. It could be applicable in a clinical setting of developing countries. However, the efficacy of this regimen should be further studied.

Key words : HIV, Zidovudine, late pregnancy

The number of infant infected with HIV via vertical transmission route is increasing with the ever expanding AIDS pandemic. The prevalence rate of Thai HIV-1 infected pregnant women was recently reported as 2% is 1993.[1] Prevention of vertical transmission is very important. According to AIDS Clinical Trial Group protocol 076 (ACTG 076), zidovudine (ZDV) use in HIV infected pregnancy can reduce vertical transmission rate from 25.5% to 8.3%.[2] However, regimen of ZDV use in ACTG 076 should not be applicable to developing countries because of its cost and complexity. Department of Obstetrics and Gynaecology,Faculty of Medicine, Ramathibodi Hospital has introduced ZDV treatment in late pregnancy to prevent vertical transmission among HIV-1 infected parturients since January 1995. The objective of this study was to evaluate safety and tolerance of ZDV use in late pregnancy.

Materials and Methods

Between January 1995 and June 1996, 35 cases of eligible HIV-1 infected pregnant women attending antenatal care at Ramathibodi Hospital were enrolled to the study willingly. They were diagnosed during a voluntary test for HIV and confirmed with Western blot technique. The eligible inclusion criterias were haemoglobin > 10 g/dL, platelet count > 100,000 /cu.mm. and negative for urine albumin and sugar. The exclusion criterias were ZDV treatment before and during this pregnancy, symptomatic HIV infection, allergy to ZDV and developed complications during this pregnancy. Each woman gave written informed consent for her participation. Because of our booking system for antenatal care, all of them were recruited before 20 weeks of gestational age and had regular follow up according to our schedule. The ZDV protocol consisted of ZDV 250 mg orally twice daily which started from gestational age 36 weeks until labour. Their compliances were observed by pill counts. No ZDV was given during intrapartum period and in newborns. No breastfeeding was recommened to all parturients. They were appointed to follow up at 6 weeks after delivery for postpartum check up and family planning. The newborns were evaluated at birth and their peripheral blood specimen were tested for HIV genome by previously described PCR technique,[3] using HIV-1 pol primer JA 17, 18, 19, 20 nested PCR. Statistical values were mean, standard deviation and percent.

Results

From January 1995 to June 1996, 35 cases of eligible asymptomatic HIV-1 infected pregnant women were recruited to the study. The characteristics of the pregnant women were shown in table 1. The mean duration of ZDV treatment was 24.6 ± 9.5 days (range 5-40 days). Based on pill count, 91.4% of HIV-1 infected parturient had complete ZDV treatment and most of them did not had any serious side effects. The most common side effect was nausea and vomiting (Table 2). The mean duration of rupture membranes and labour were 6.3 ± 4.9 and 12.1 ± 6.3 hours respectively. The mean birthweight was 3,004 ± 297.4 grams with maximum 3,560 grams and minimum 2,290 grams. The mean Apgar score at 1 minute and 5 minute were 8.5 ± 1.4 and 9.7 ± 0.3 respectively. Most of them were delivered by normal delivery (Table 3). No HIV-1 genome was detected from peripheral blood of newborns at birth. No congenital anomaly, birth asphyxia and stillbirth were observed in this study. No maternal morbidity was observed during the postpartum period.

Table 1. Characteristics of HIV-1 positive pregnant women

Characteristics (N = 35)	
Mean age (year)	25.8 ± 4.6
Mean weight at delivery (kg)	61.9 ± 7.7
Mean height (cm)	154.1 ± 5.7
Mean haemoglobin (g/dL)	11.4 ± 1.2
Mean ANC (visit)	8.5 ± 2.3
Gravida	
1	23(65.7%)
>1	12(35.3%)
Address	
Bangkok	30(85.7%)
Other	5(14.3%)

Table 2. Compliance and side effects of ZDV use

Variables (N = 35)	Number	Percent
Compliance		
Complete ZDV use	32	91.4
Incomplete ZDV use	3	8.6
Side effects		
Nausea/Vomiting	4	11.4
Headache	3	8.6
None	28	80.0

Table 3. Type of delivery

Type of delivery	Number	Percent
Normal	27	77.1
Forceps extraction	1	2.9
Vacuum extraction	2	5.7
Caesarean section	4	11.4
Breech delivery	1	2.9
Total	35	100.0

Discussion

Using sensitive techniques of viral detection (PCR and viral culture), new working definitions for early versus late infection were proposed : an early (in utero) infection would correspond to the detection of HIV-1 genome by PCR or viral isolation within 48 hours of birth, a late (intrapartum) infection would correspond to negative PCR/viral isolations during the first week of life and becoming positive after day-7 in nonbreastfed infants.[4]

Administering ZDV to the mother and infant following ACTG 076 protocol regimen is proved to reduce vertical transmission.[2] Later studies also confirmed these results.[5-9] However, in developing countries, ACTG 076 protocol presents great challenges because of its cost and complexity. Thus, several simpler interventions are being explored including short course of ZDV treatment. We have conducted a study of oral ZDV administered in late pregnancy to HIV-1 infected pregnant women since January 1995. From our previous study it was revealed that most of them accepted to have ZDV treatment in pregnancy in order to reduce vertical transmission.[10] However, safety and tolerance of ZDV use in late pregnancy need to monitor and evaluate. From the study, it was shown that ZDV treatment in late pregnancy had better compliance with less side effects and morbidity when it was compared to ACTG 076 protocol. There were no any adverse effects on newborns who exposed to zidovudine during late pregnancy. Moreover, we could not detect HIV-1 genome with PCR technique in the newborns. This evidence suggested that zidovudine treatment in late pregnancy could prevent in utero transmission.

In summary, zidovudine treatment in late pregnancy is safe, well accepted and tolerated by HIV-1 infected parturients. It is applicable in a clinical setting. Although these results are preliminary, this regimen seems to reduce in utero transmission. However, further study should be conducted by following these newborns up to 18 months to assess its efficacy and long term side effects.[2]

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OBSTETRICS

The Study of Correlation between Sound Provoked Test (SPT) and Nonstress Test (NST)

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ABSTRACT

Objective To correlate the sound-provoked fetal movement (SPT) detected by ultrasound with the nonstress test (NST).

Design Cross-sectional study.

Setting Maternal-Fetal Medicine Unit, Department of Obstetrics and Gynaecology, Faculty of Medicine, Chiang Mai University, Thailand.

Subjects and methods From 1st October 1993 to 1st January 1995, both SPT and NST were performed in the same setting in 1,017 occasions on high-risk pregnancies. The SPT test was defined as reactive (normal) when at least one fetal movement was sonographically observed and nonreactive (abnormal) when no fetal movement was detected after the sound-provoke was applied to the fetus.

Results It was found that SPT was an accurate test in detection of reactive NST with high specificity of 96.67%, however, the sensitivity of the test was rather low (34.14%).

Conclusion Objectively detected sound-provoked fetal movement may be used as a simple and rapid method of evaluating antenatal surveillance in hight risk situation where an ultrasound is availatbe.

Key words : sound-provoked, nonstress test, antenatal fetal surveillance

Monitoring gross fetal body movement has gained worldwide attention as a method for evaluating fetal health.[1,2] The healthy fetus may be inactive as a result of sleep state for periods of up to 60 minutes.[3] Gagnon R et al examined effects of a 5 second external vibratory acoustic stimulus on fetal breathing and gross body movement patterns. There was a significant but delayed increase in the incidence of gross fetal body movements that persisted for 1 hour after the stimulus.[4,5] Maternal perception of sound-provoked fetal movement was also a reliable method of evaluating antenatal fetal well-being,[6-8] but there is still no objective recording.

The mother's registering of fetal activity near term was reported as 87% of motions recorded by an electromagnetic device[9] and 82% of all trunk and lower limb motions viewed sonographically.[10] There was also a positive relation between perceived fetal activity and that viewed by real-time ultrasound scanning.[11,12]

This study was conducted to correlate the sound-provoked fetal movement (SPT) detected by ultrasound to improve fetal visualization with the nonstress test (NST).

Materials and Methods

The study was undertaken at Maternal-Fetal Medicine Unit, Department of Obstetrics and Gynaecology, Faculty of Medicine, Chiangmai University, Thailand, from 1st October 1993 to 1st January 1995. A total of 1,017 individual tests have been performed on high-risk pregnancies. We obtained informed consent after explaining the procedure of the test. Age, parity, gestational age, and indications for testing were recorded.

Both SPT and NST were performed in all cases. The patients were placed in a semi-Fowler's position. Fetal acoustic stimulation was accomplished with a single pulse of sound 3 seconds in duration applied transabdominally over or near the fetal vertex using a Corometrics Model 146 fetal acoustic stimulator, sound level 82 dB at 1metre in air, the fundamental frequency of 80 Hz and the harmonics range of 20-9,000 Hz (Corometrics Medical Systems, Connecticut, USA), during continuous ultrasound visualization using Aloka SSD 680 by single ultrasonologist. Fetal movement resulting in visualization of the desired anatomy within 30 seconds of administering the sound pulse was considered a positive response (a normal test). If there was no fetal movement observed within 30 seconds, the stimulation was repeated up to three times. If there was still no fetal movement observed, the test was considered negative response (an abnormal test). The NST was performed immediately after the vibroacoustic stimulation with fetal heart rate monitor 145 (Corometrics, Connecticut, USA). All the fetal heart rate tracings were interpreted blindly by one independent perinatologist, who did not have any clinical information on the result of the SPT. The NST was considered reactive if there were two or more fetal heart rate accelerations of at least 15 bpm, lasting 15 seconds, in any 20 minute period. One prolonged acceleration of the fetal heart rate of at least 15 bpm lasting more than two minutes was also interpreted as reactive. If these criteria were not met in 40 minutes of monitoring, the test was interpreted as nonreactive, and additional testing with either the contraction stress test (CST), biophysical profile (BPP), or Doppler velocimetry was further performed.

Results of sound-provoked fetal movement test detected by ultrasound would be correlated to results of the NST.

Results

SPT and NST were performed on 1,017 occasions in 666 high-risk pregnancies. Table 1 presents the main risk factors in these patients. Of the total population 13.0% were 28-32 weeks, 58.1% were 33-37 weeks, 26.6% were 38-41 weeks, and the remaining 2.3% were ≥ 42 weeks. Table 2 shows the results of the sound-provoked fetal movement detected by ultrasound in relation to the results of the NST. On 59 occasions (5.8%) the response to vibroacoustic stimulation was negative. There was fetal movement detected by ultrasound in 958 occasions (94.2%) ; 83.4% detected with the first stimulation, 6.3% with the second, 2.9% with the third, and only 1.6% with the fourth stimulation.

Table 1. Main risk factors in 1,017 occasions included in the study

Risk factors	Frequency	%
Postterm	19	1.9
Suspected intrauterine growth retardation	625	61.5
Decreased fetal movement	147	14.5
Pregnancy-induced hypertension	63	6.2
Chronic hypertension	7	0.7
Diabetes mellitus	45	4.4
Heart disease	14	1.3
Others	97	9.5
Total	1,017	100.0

Table 2. Result of 1,017 paired sonographically observed sound-provoked fetal movement in relation to the results of nonstress test

Sonographically observed Sound-Provoked Fetal Movement	Result of Nonstress Test		Total
	Nonreactive	Reactive	
Absent	28	31	59 (5.8%)
Present	54	904	958 (94.2%)
Total	82 (8.1%)	935 (91.9%)	1,017 (100%)

Of the 958 occasions which detected the fetal movement, 904 (94.4%) had a reactive NST, whereas 54 (5.6%) had a nonreactive NST. Of the 59 occasions with absence of fetal movement, 28 (47.5%) had a nonreactive NST. Twenty-eight of the 82 nonreactive NST were predicted by absence of fetal movement in response to vibroacoustic stimulation, giving a sensitivity of 34.1%. Of 935 reactive NST, 904 were predicted by the detection of fetal movement in response to the stimulus, giving a specificity of 96.7%. Twenty-eight of 59 occasions with absence of fetal movements had nonreactive NST, giving a predictive value of a positive (abnormal or nonreactive NST) test of 47.5%. The predictive value of negative (normal or reactive NST) test was 94.4 (904/958).

Discussion

Recording gross fetal body movement may serve as an indirect mean of evaluating central nervous function and integrity since the coordina-

tion of whole body motion requires complex neurologic control.[1] External vibratory acoustic stimulation may provoke increased fetal activity and an associated increase in heart rate baseline. This vibratory acoustic device was helpful in increasing the likelihood of a reactive nonstress test pattern and a reduction of test time.

Attempts had been made to evaluate the value of maternal perception of sound-provoked fetal movement as a test of antenatal fetal health compared with a nonstress test, and maternal perception of sound-provoked fetal movement was found to be a method for evaluating fetal well-being.[6-8] But only 82-87% of fetal motions was reported by mother's registering.[9,10] This study was conducted to evaluate the value of sound-provoked fetal movement detected by ultrasound in an effort to improve visualization of the fetal movement.

We found that sound-provoked fetal movement visualized by ultrasound, when correlated with the NST, had high specificity (96.7%) and negative predictive value (94.8%) which meant that NST was almost always reactive when fetal movement was visualized. The results confirmed the previous reports of subjectively maternal perception of sound-provoked fetal movement.[6-8] Sensitivity, specificity, positive predictive value, and negative predictive value for sound-provoked fetal movement in each study were compared in table 3. The objectively detected sound-provoked fetal movement may be used as a simple and rapid method of evaluating fetal health in high risk pregnancies where an ultrasound is available, but the absence of detection of fetal movement does not always indicate fetal compromise.

Table 3. Comparison between sensitivity, specificity, positive predictive value, and negative predictive value for sound-provoked fetal movement in each studies

	Westgren[6] (subjective)	Arulkumaran[7] (subjective)	Chutiwongse[8] (subjective)	This study (objective)
Sensitivity (%)	100	76.9	35.0	34.1
Specificity (%)	89	92.8	99.6	96.7
Positive predictive value (%)	19	11.4	77.8	47.5
Negative predictive value (%)	100	99.7	97.4	94.4

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OBSTETRICS

A Preliminary Report on Mid-trimester Routine Ultrasonographic Screening in Ramathibodi Hospital

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ABSTRACT

Objective To evaluate the detection rate and type of abnormal findings by mid-trimester routine ultrasonographic screening.

Design Prospective descriptive study.

Setting Department of Obstetrics and Gynaecology, Faculty of Medicine, Ramathibodi Hospital.

Subjects All primigravida of less than 30 years old who attended the antenatal care clinic at Ramathibodi Hospital in 1994.

Main outcome measures Number and percentage of abnormal findings detected by routine ultrasonographic screening.

Results Twelve percent of all women screened had abnormal findings. This included 3 malformations (0.2%), 3 ectopic pregnancies (0.2%), 5 pregnancies with ovarian tumour (0.34%), 5 pregnancies with myoma uteri (0.34%), 7 molar pregnancies (0.47%), 12 twin pregnancies (0.81%), 23 placenta previa (1.54%), 73 abortions (4.95%) and 57 cases who did not pregnant (3.83%).

Conclusion Mid-trimester routine ultrasonographic screening in pregnant women seems to be of benefit and cost effective in Ramathibodi hospital.

Key words : mid-trimester, ultrasound

The subject of routine ultrasonographic screening at mid-trimester during pregnancy remains controversial. Its usefulness includes accurate dating of gestational age, early detection of multifetal pregnancy, detection of potential cases of placenta previa, detection of fetal mal-

formation and detection of abnormal pregnancies such as hydatidiform mole and dead fetus in utero. Accurate dating of gestational age also makes subsequent diagnosis of intrauterine growth retardation easier. These seemingly obvious advantages had led to wide spread implementation of screening programme across the continents. Historically the first large scale screening programme was introduced twenty years ago in Sweden where a two-stage examination is offered to the pregnant population ; the first is at 19 weeks and the second at 32 weeks.[1] This was adopted by the Federal Republic of Germany in 1980 and by Austria in 1988. In 1986 Norway and Iceland on the other hand recommended the one-stage mid-trimester screening programme to their populations.

The increasing implementation of routine ultrasonographic screening programme into many obstetric units worldwide had led to the evaluation of its usefulness and cost effectiveness. Many authors doubt its ability to reduce perinatal mortality and improve pregnancy outcome.[2-5] In 1984 two contradicting reports were published. One, in Great Britain a working party of the Royal College of Obstetricians and Gynaecologists favoured an one-stage ultrasonographic screening.[6] The other, from the United States a panel from the National Institute of Health concluded that routine ultrasonographic screening was not recommended.[7]

The Department of Obstetrics and Gynaecology at Ramathibodi hospital is responsible for nearly 8,000 births annually. Towards the end of 1993 we contemplated on offering an one-stage ultrasonographic screening to our pregnant population. Being aware of the controversy surrounding the usefulness and cost effectiveness of the screening programme, not to mention the possible adverse effects on the fetus[8,9] which to date is only theoretical, we decided to carry out a pilot study, performing routine one-stage examination on a low risk group. The objective of this study was to evaluate the detection rate and types of abnormal findings. The results of this study could also help us in working out the feasibility of implementing screening programme for the whole pregnant population.

Table 1. Results of mid-trimester routine ultrasonographic screening

Results	Number	%
Normal single viable fetus	1,281	86.03
Abortion	73	4.95
Not pregnant	57	3.83
Placenta previa	23	1.54
Twin pregnancy	12	0.81
Molar pregnancy	7	0.47
Pregnancy with myoma uteri	5	0.34
Pregnancy with ovarian tumour	5	0.34
Ectopic pregnancy	3	0.20
Fetal anomalies	3	0.20

Materials and Methods

The study period was from January to December 1994. Our antenatal clinic runs on Monday, Wednesday and Friday from 8 : 00 - 12 : 00 a.m. Prior to the study we were already providing ultrasonographic services to 15 - 20 women per day with indications. The study group included all primigravida of less than 30 years old. A level one ultrasonographic scanning was performed at 18 - 22 weeks by Obstetricians using a Hitachi EUB-415 scanner. Measurements taken included biparietal diameter, femur length and abdominal circumference. The placenta site and amount of amniotic fluid were noted and fetal malformation searched for. In cases of uncertain abnormal findings the women were reviewed by a panel of Obstetricians with repeated scans on Thursday afternoon when more time is available. The diagnosis and management thereof is then decided in consultation with senior Obstetricians.

Results

During the studied period 1,489 women were screened at 18-22 weeks' gestation. This represents an average of 10 women per clinic. As we also performed approximately 20 indicated scans each morning, the time spent on each woman was 5 - 10 minutes. Results of the ultrasonographic screening are shown in table 1.

Twelve percent (N = 188) of all women screened had abnormal findings. These included 57 women who were in fact not pregnant. There were three anencephaly (0.2%), all of which were terminated subsequently. There was no malformation which was missed by routine ultrasonographic screening. Of all the 23 women who were found to have placenta covering the cervical os at routine ultrasonographic screening were subsequently shown to have placenta previa at term.

Discussion

In developed countries the three leading contributing factors to perinatal mortality are congenital malformation, prematurity and intrauterine growth retardation. Our department for many years now has had low perinatal mortality rate of 6 - 8/1,000 livebirths,[10] a figure comparable to that of developed countries. We are no longer presented with problems of neonatal sepsis, intrapartum asphyxia or traumatic delivery. To further improve our maternal-perinatal care it was agreed that routine ultrasonographic screening might be of benefit.

Our pilot study shows that even in a low risk group, appreciable number of abnormal findings were detected. In these cases routine ultrasonographic screening at mid-trimester removed the doubt of uncertaining of gestation. The incidence of fetal malformations is 0.2%. This is fewer than the usual 0.5-1% quoted and could be explained by our selected low risk study group. Despite the fact that our study group only accounts for 20% of the total number of deliveries in 1994, the number of anomalies which were represented in perinatal mortality rate decreases to 8 as compare to 16 in 1991 and 12 in 1993. We therefore expect this number to decrease further if the whole pregnant population was screened. It is surprising to find that 4 percent of all patients were not pregnant. This reflects the inefficiency of the booking system. In our unit most patients usually booked very early in pregnancy (less than 12 weeks). Bimanual pelvic examination is not routinely performed at the first visit and since the second visit is at about 20 weeks when routine ultrasonographic examination is carried out, many patients who were never pregnant would only be detected at this ultrasound examination.

As mentioned earlier published works which

do not recommend routine ultrasonographic screening programme based their conclusions on their findings that routine ultrasonographic screening failed to reduce perinatal mortality and improve pregnancy outcome and therefore not cost-effective. There are several reasons for such findings. Many of the malformations were detected after 24 weeks when legal termination of pregnancy is not available.[2] Many of the women who were carrying abnormal fetuses chose to continue their pregnancies.[2] Some of the anomalies detected are amenable to medical and surgical treatment.[5] We believe the situation in our population is different. From our experience throughout the years all the parents who were informed that the fetus they were carrying had major malformations chose to terminate the pregnancies. Many of the malformations which may be successfully treated in developed countries are usually fatal here in our country.

As in any screening programme the most important issue which we have not addressed here is the cost effectiveness. The most recent study which attempts to tackle this is from South Africa.[11] This is the first randomized controlled trial in a developing country. The authors conclude that routine ultrasonographic screening is expensive and more selective use of ultrasound is not accompanied by increased adverse perinatal outcome.

Among the various parameter used in assessing the cost effectiveness the most difficult if not an impossible factor to evaluate is the psychological trauma inflicted on the parents on learning that they are carrying abnormal pregnancies. The choice lies between the tremendous grief of an unexpected birth of a severely malformed baby at term in unscreened women and the psychological trauma of going through mid-trimester termination of pregnancy after a malformation is discovered during routine ultrasonographic screening.

The results of other studies which have shown that routine ultrasonographic screening can detect fetal malformations and reduce perinatal mortality and morbidity,[12-14] together with the preliminary result of this pilot study have encouraged us to decide to implement routine ultrasonographic screening programme to the whole pregnant population. Only when this has been carry out for sometime then we would be able to fully assess the impact on whether we could improve pregnancy outcome and reduce our perinatal mortality rate still further.

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XII th SCIENTIFIC AND ANNUAL

RTCOG MEETING

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GYNAECOLOGY

Effects of Tibolone in Thai Post-menopausal Women

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ABSTRACT

Objective To assess the effects of tibolone on climacteric symptoms, serum levels of sex hormones (FSH, LH, E_2), lipids and calcium as well as the bone mineral density in Thai post-menopausal women.

Design Prospective study.

Setting Menopause clinic, Chulalongkorn Hospital.

Subjects Thirty-one post-menopausal women without contraindication to hormonal replacement therapy were recruited. A daily oral dose of 2.5 mg tibolone was administered to all subjects for 6 months.

Main outcome measures Climacteric symptoms were assessed periodically. Serum levels of sex hormones, lipids and calcium as well as the bone mineral density were measured at the beginning and the end of the study.

Results Climacteric symptoms decreased over the study period. There was no significant change in the levels of sex hormones, total cholesterol, apolipoprotein A and B. A reduction in the levels of HDL and calcium was observed. Bone mineral density remained unchanged.

Conclusion Tibolone is suitable for the treatment of climacteric complaint and also potentially capable to prevent post-menopausal bone loss.

Key words : tibolone, post-menopausal women

In the past, menopausal symptoms were considered unpleasant but inevitable part of woman's life which had to be endured in silence. The treatment of the symptoms associated with the climacteric syndrome, namely: hot flushes, sweating, paresthesia, insomnia, loss of libido, irritability, dizziness, depression, muscle and joint pain, fatigue, palpitations and psychological instability included administration of estrogens, such as conjugated estrogens and estradiol or

one of its ester derivatives. However, long-term administration of these estrogens as a monotherapy (unopposed estrogen therapy) carries the risk of overstimulating the endometrium. The addition of a progesterone at regular intervals protects against endometrial overstimulation, but also results in regular post-menopausal withdrawal bleeding.[1,2] This regular withdrawal bleeding at the end of the progesterone cycle in conventional hormonal replacement therapy (HRT) is unacceptable to many women.[3] This fact leads to a need for a new drug that is able to alleviate these climacteric complaints and prevent bone loss in osteoporotic women, while not stimulating the endometrium, not having negative effects on the cardiovascular system and not increasing the risk of malignancies.[4]

Tibolone is a steroid compound formulated by Organon company. This compound is structurally related to the progestogens, norethynodrel and norethisterone, but has one additional double bond and additional 7-methyl group. Pharmacological studies in laboratory animals have demonstrated that the drug exerts mild estrogenic effect. Hormonal experiments with laboratory animals have shown the estrogenic effect of tibolone to be 1/50 that of ethinyl estradiol, the progestogenic effect to be less than half of that of norethynodrel and less than 1/8 that of norethisterone, the androgenic effect to be 3 times weaker than that of norethisterone, and the ovulation inhibiting effect to be the same as that of norethynodrel and 20 times greater than that of norethisterone, indicating a relatively strong central effect.[5,6] Other experiments with laboratory animals have shown tibolone to be able to reduce the frequency of ovariectomy-induced hot flushes, and inhibit bone loss.[7]

Some clinical studies with human subjects have shown tibolone to be able to reduce the symptoms of the climacteric syndrome as well as post-menopausal skeletal demineralization,[8] while not exerting any negative side effects such as endometriotrophic effects or post-menopausal bleeding.[9] However, these studies were done in European women.

The objective of this study was to assess the effects of tibolone on climacteric symptoms, bone mineral density, serum levels of sex hormones, lipids and calcium in Thai post-menopausal women.

Materials and Methods

Thirty-one post-menopausal women were recruited for the trial on the basis of the following criteria :

- voluntarily attended the menopause clinic at Chulalongkorn Hospital,
- time since has had the menopause for longer than one year,
- no hormone-dependent tumours,
- no cardiovascular or cerebrovascular disorders,
- no vaginal bleeding due to unkonwn causes,
- no severe liver or kidney disorders,
- no treatment for climacteric symptoms within the last 3 months.

A daily oral dose of 2.5 mg tibolone (Livial^{R}) was administered to each of the subjects for a period of 6 months. This dose was chosen on the results of a pre-test dose which had shown 5 mg/day to induce vaginal bleeding and 1.25 mg/day to be insufficient in alleviating vasomotor symptoms.

All 12 symptoms associated with the climacteric syndrome (mentioned in the introduction) were assessed by asking the women to rate the severity of each symptom by assigning a score of 0-3.

The scores of these 12 symptoms were assessed on four occasions during the study period : day 0, day 30 (1month), day 90 (3 months), and day 180 (6 months).

The incidence of vaginal bleeding was recorded monthly. Serum sex hormones : follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E_2), serum lipids : total cholesterol, high-density lipoprotein (HDL), apolipoprotein A, apolipoprotein B and calcium were measured and recorded at day 0 and day 180. The bone mineral density of the lumbar spine and hip was measured by dual photon absorptiometry at the beginning and the end of the study. The body weight and blood pressure was recorded 3 times (day 0, day 90 and day 180).

Satistical analysis were expressed as mean with standard deviation (SD) and percentage as appropriate. The differences in the means were compared by student t-test. The P value of < 0.05 was considered as statistical significance.

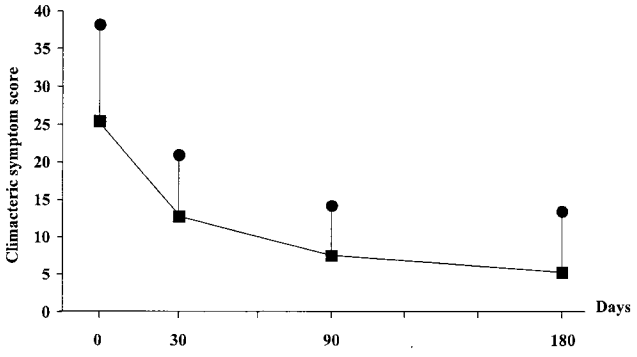

Fig. 1. Mean (+ SD) values for total climacteric symptom score in the tibolone treated patients (N = 31, P < 0.05).

Results

The women recruited ranged in age from 47-60, with a mean age of 53.3. The average number of years since the menopause was 4.3.

Climacteric symptom : Total scores of the 12 climacteric symptoms steadily decreased over the 6 month study period in almost all of the women (Fig. 1).

Vaginal bleeding : Vaginal bleeding occurred in 6 women while taking Tibolone in the first month. After that, the number of women experiencing vaginal bleeding decreased. There was no vaginal bleeding observed after the fourth month (Table 1).

Body weight and blood pressure : At the pre-trial examination, the body weight and blood pressure of all women admitted to the trial were found to be within the normal range. There were no significant changes in the mean values of body weight and blood pressure during the 6 month study period (Table 2).

Serum sex hormones : The mean values of serum FSH, LH and E_2 levels at the beginning and the end of the study are shown in Fig. 2. While no change was observed in the serum E_2

Table 1. The number of women experiencing vaginal bleeding (N = 31)

	Day						
	0	**30**	**60**	**90**	**120**	**150**	**180**
Number of women	0	6	3	1	1	0	0
Percent	0	19.4	9.7	3.2	3.2	0	0

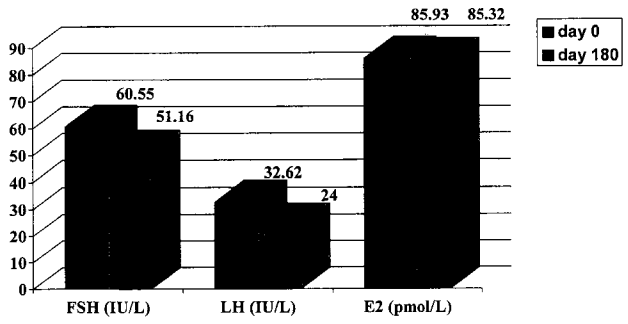

Fig. 2. The serum levels of sex hormones (N = 31).

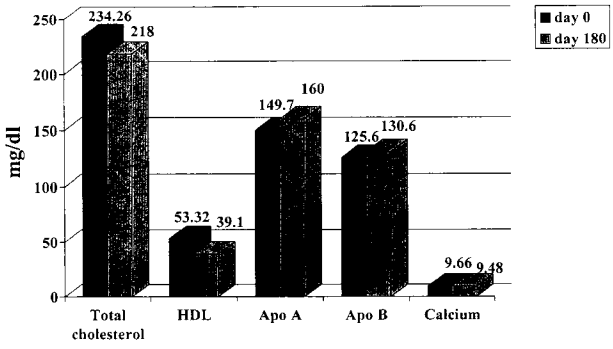

Fig. 3. The serum levels of lipids and calcium (N = 31).

level, there was a drop in the levels of serum FSH and LH, but these changes had no statistical significance.

Serum lipids and calcium levels : Fig. 3 shows the mean values for serum total cholesterol, HDL, apolipoprotein A, apolipoprotein B and calcium levels. There was a significant reduction in the levels of serum calcium and HDL. A reduction in the serum total cholesterol and a rise in the serum apolipoprotein A were observed although there was no statistical significance.

Bone mineral density : The data on the bone mineral density measured by dual photon absorptiometry in the lumbar spine and hip are shown in Table 3. During the 6 month study period, no significant change in these values was found.

Discussion

A rational approach to the therapy of climacteric symptoms and to the prevention of long-term sequelae of menopause like osteoporosis and cardiovascular accident, is the subsitiution of various sex hormones. The combination of estrogen-progestogen therapy has been recommended and applied successfully, but sometimes leads to regular or irregular bleeding especially during the initial months of treatment. These bleedings are regarded as unacceptable by many post-menopausal women, leading to poor compliances and high drop-out rates.

The benefits and risks of tibolone therapy in post-menopausal women have been shown in many recent studies. Our study clearly indicates that tibolone, orally administered in a daily dose of 2.5 mg, is an efficient mean of inhibiting the climacteric symptoms (Fig. 2). This finding is in agreement with previously published data.[5,6,8] Vaginal bleeding occurred in six cases during the first month of treatment, four of whom have had menopause within two years. Pathological diagnosis of sampling endometrium during bleeding revealed an atrophic endometrium. There was no vaginal bleeding observed after the fourth month (Table 1). The data presented shows that, unlike preparation containing estrogen, tibolone does not cause endometrial proliferation, which is of considerable clinical importance. This therapy does not cause weight gain or affect blood pressure during the study period of 180 days (Table 2).

Recent studies showed that at a dose of 2.5 mg/day tibolone significantly suppressed plasma FSH, and to a lesser extent, LH levels in climacteric patients.[6,7] In our study, there was

Table 2. Body weight and blood pressure (N = 31)

	Day			
	0	**30**	**90**	**180**
Body weight (kg)	58.1	57.9	59.2	58.1
Blood pressure (mmHg)				
Systolic	116 ± 13.1	116 ± 15.6	113 ±15.7	116 ± 17.1
Diastolic	75 ± 11.3	74 ± 1.0	75 ± 9.3	73 ± 6.6
P-value	-	NS	NS	NS

NS = No statistical significance

Table 3. The bone mineral density (N = 24)

	Day		
	0	**180**	**P-value**
Spine (g/cm^2)	0.86 ± 0.14	0.83 ± 0.10	NS
Hip (g/cm^2)	0.78 ± 0.12	0.78 ± 0.10	NS

also a drop in the level of FSH and LH, however, this finding was not statistically significant. The effect of tibolone on lipid metabolism appears to be complex. In short term studies, tibolone induced a clear decrease in HDL and apolipoprotein A1 in young oophorectomized women. However, long term clinical data showed no difference in HDL level in comparison with control group while triglycerides and very low density lipoprotein (VLDL), and cholesterol were significantly decreased.[10] During our six-month trial period, we observed a significant decline in HDL level which is in agreement with other studies. However, serum apolipoprotein A was observed to be increased but of no statistical significance. To clarify this finding, we recommended more study cases and longer period of follow up. Serum calcium was shown to be decreased with statistical significance. This finding again needs more cases with longer follow-up period, moreover, urine calcium concentration should be examined instead of serum calcium.

Tibolone, in several studies, was found to be a bone-active compound with anti-resorbing as well as anabolic activity.[8,11] Long-term prevention of bone loss as well as curative treatment of post-menopausal osteoporosis was shown in these studies. We found, from our study, that the bone mineral density of the lumbar spine and hip did not change during the six-month trial period. However, we need more time to follow up the cases.

In summary, tibolone appears to be particularly suited for the treatment of the

climacteric complaint in view of its efficacy in alleviating hot flushes and associated complaints, lack of stimulating effect on the endometrium, and capacity to prevent post-menopausal bone loss. Further studies should be designed to complete in clinical profile of this new drug for the post-menopausal patients.

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GYNAECOLOGY

Efficacy of Intranasal Buserelin for Preoperative Treatment of Uterine Leiomyomas

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ABSTRACT

Objective To study the efficacy of intranasal buserelin for preoperative treatment of uterine leiomyomas.

Design Open non-comparative study.

Setting Reproductive endocrine unit, Ramathibodi hospital.

Subjects Seventeen patients with symptomatic uterine leiomyomas.

Interventions All patients were treated with intranasal buserelin 900 ug/day for 12-16 weeks. Hysterectomy was performed within 2 weeks after discontinuation of buserelin treatment.

Main outcome measures Clinical symptoms, volume of uterine leiomyomas and adverse effects of the treatment.

Results Two patients were excluded from the study, one had severe headache four days after drug used, the other was lost to follow up with unknown reason. The mean volume of uterine leiomyoma decreased by 33% after 12 weeks of treatment from mean pretreatment volume of 274.94 ± 37.45 cm^3 to 182.46 ± 16.78 cm^3 ($P < 0.05$).

Nine of fifteen patients experienced more than 25% reduction in leiomyoma volume. Tumour related symptoms (dysmenorrhea, pelvic pain and pressure symptoms) decreased in all cases after 8 weeks of treatment.

Conclusion This preliminary results demonstrate the efficacy of intranasal buserelin in reduction of uterine leiomyoma and alleviation of clinical symptoms. The usefulness and cost-benefit of GnRH-a preoperative treatment of uterine leiomyoma should be evaluated further.

Key words : leiomyoma, GnRH-a

Uterine leiomyomas are the most common benign tumour of pelvic neoplasm. Although its aetiologic cause is unknown, many evidences have suggested that this tumour is estrogen dependent.[1,2] Continuous administration of gonadotropin releasing hormone agonist (GnRH-a) could suppress the gonadotropins and sex steroids production and subsequently reduce the growth of uterine leiomyomas.[1,2] After the first report of reduction of leiomyoma size by the GnRH-a therapy was published in 1983,[3] many studies have confirmed the reduction of leiomyoma volume and alleviation of tumour related symptoms.[4-11] Because the regrowth of tumour occurs rapidly after discontinuation of the drug using, so this therapy has been used as a preoperative treatment. In Thailand, GnRH-a has been available for several years, but no study of its efficacy for the treatment of uterine leiomyoma in Thai patients has been reported. Buserelin is a GnRH-a which glycine at position 6 and 10 of the natural GnRH molecule are replaced by D-serine and ethylamide respectively. Its potency is 20 times more than the natural GnRH.[9]

The objective of this report was to study the efficacy of intranasal buserelin for preoperative treatment of uterine leiomyomas in Thai women.

Materials and Methods

This study was open, non-comparative clinical trial. Seventeen patients with symptomatic leiomyomas were enrolled to the study. The inclusion criteria were as follows :

1) had uterine leiomyoma with related symptoms justified for surgical therapy.

2) had one leiomyoma at least more than 3 cm in diameter by ultrasound.

3) were not pregnant and not desirous of future pregnancies.

4) had haemoglobin equal to or more than 8 g/dL and had no serious infectious disease, history of depression, abnormal liver function and impaired renal function.

Each patient received intranasal buserelin (Suprefact E^R, Hoechst, Germany) 900 μg/day (300 μg x 3) for 12-16 weeks. The treatment was started in the first week of menstrual cycle. Patients were instructed to use the record form of buserelin administration. The size of largest leiomyoma was measured by abdominal ultrasound in three dimensions by two gynaecologists using 3.5 MHz transducer (Aloka SSD 1200, Tokyo, Japan) before treatment and every four weeks after treatment. The leiomyoma volume was calculated by formula $0.523 \times D_1 \times D_2 \times D_3$ (D_1, D_2, D_3 : diameter of leiomyoma in three dimensions). Serum estradiol (E_2) concentration was determined by using radioimmunoassay method before treatment and at 4, 8 weeks after treatment. Clinical symptoms and adverse effects were recorded every four weeks. An unpaired t - test was used to test the difference of leiomyoma volume between pretreatment and after treatment.

Results

Two patients were excluded from the study. One had severe headache four days after drug used and the symptom disappeared with discontinuation of drug administration, the other was lost to follow up after 8 weeks of treatment with unknown reason. Data of the remaining fifteen patients who completed the study were analysed. Table 1 showed patient characteristics. All patients were in the reproductive age. The mean body mass index (BMI) was 23.12 ± 0.77 kg/m^2 (range 19.13 - 28.30) .

Tumour reduction was observed in all but one patient. The mean volume of leiomyoma

decreased by 33% from pretreatment volume of 274.94 ± 33.45 cm^3 (range 91.58 - 695.28) to 182.46 ± 16.78 cm^3 (range 61.50 - 288.22) after 12 weeks of treatment (Fig. 1). Most patients (53.3%) experienced 25 - 50% reduction in leiomyoma volume, one had more than 50% reduction (Table 2). Patient symptoms such as pelvic pain (5 cases), dysmenorrhea (6 cases) and menorrhagia (9 cases) disappeared after 8 weeks of treatment (Table 3). Nevertheless, vaginal bleeding was observed in 2, 5 and 3 patients at the end of 4, 8 and 12 weeks respectively.

In 7 out of 15 patients, serum E_2 decreased to post-menopausal level. Of these, 3 patients decreased after 4 weeks of treatment and the other 4 occurred after 8 weeks. However, the mean serum estradiol before and during treatment did not differ significantly.

In one third of the patients, no gonadal suppression was observed during treatment. Despite of no gonadal suppression, tumour

Table 1. Patient characteristics

	Mean ± SEM	Range
Age (yr)	40.07 ± 1.20	28 - 46
Height (cm)	154.07 ± 1.39	149 - 168
Weight (kg)	54.89 ± 2.00	45 - 68
BMI (kg/m^2)	23.12 ± 0.77	19.13 - 28.30

SEM - standard error of mean

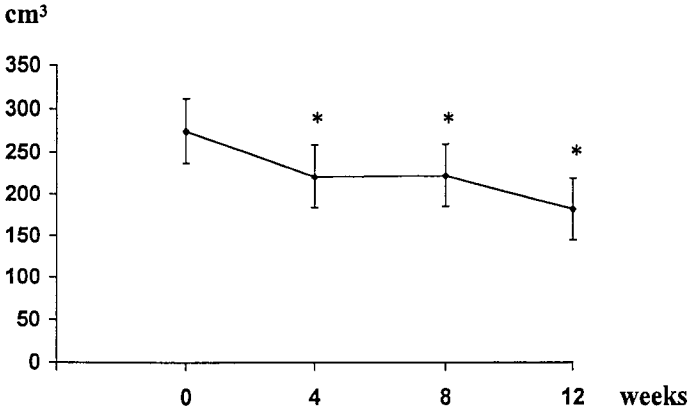

Fig. 1. Changes in volume of uterine leiomyoma during buserelin treatment.
* $P < 0.05$ as compared to pretreatment

Table 2. Number of patients in different degree of tumour reduction

Degree of tumour reduction	No.	%
< 0.1%	1	6.7
0.1 - 25%	5	33.3
25 - 50%	8	53.3
> 50%	1	6.7
Total	15	100.0

Table 3. Number of patients with uterine leiomyoma related symptoms

	Duration of treatment (weeks)			
	0	4	8	12
Pelvic pain	5	2	-	-
Dysmenorrhea	6	3	-	-
Menorrhagia	9	1	-	-
Vaginal bleeding	-	2	5	3

reduction occurred in 4 of 5 patients.

Two patients had hot flushes. No other adverse symptoms were reported in the fifteen patients.

Discussion

The result of this study confirms previous studies that GnRH-a effectively reduce volume of uterine leiomyoma in most patients. The reduction of mean volume of uterine leiomyoma was observed by 33%. The magnitude of tumour reduction in the present study is comparable to the others using intranasal buserelin in the same dose for 12 weeks of therapy.[6,10] However, the magnitude of volume reduction in this study is less than the others which have demonstrated the reduction of 44-50% after 3 months of subcutaneous long acting GnRH-a usage. [5,7,8,11] In the present study, 9 of 15 patients (60%) experienced more than 25% of volume reduction, and only one patient (6.7%) experienced more than 50% of volume reduction while Friedman et al[7] have demonstrated that 15 of 18 patients (83%) had more than 25% of volume reduction and 4 of 18 (22%) had more than 50% of volume reduction after using subcutaneous leuprolide acetate depot, long acting GnRH-a, for 12 weeks of therapy. These have shown that the efficacy of long acting GnRH-a is superior to the short acting one, which can be explained by the difference of bioavailability, especially absorption of two forms of the drugs. The absorption of intranasal buserelin is less than 5%, thus the serum drug concentration is so low.[12] The gonadal suppression is achieved more complete in long acting than short acting GnRH-a. Therefore, more reduction of tumour volume should be observed in the long acting one. The study of Friedman et al,[5] in which comparison of using subcutaneous and intranasal leuprolide in the treatment of uterine leiomyoma has demonstrated that significant reduction of tumour volume was achieved in the subcutaneous group, but no reduction of tumour volume was occurred in the intranasal group, can confirm the explanation.

Although only seven patients had serum E_2 concentration below 30 pg/ml, but tumour reduction was observed in 14 of 15 patients, especially 4 of 5 patients had tumour volume reduction despite of no gonadal suppression. So the gonadal suppression in different degree in most patients with the fluctuation of E_2 concentration during the treatment should be considered. This fluctuation of E_2 occurred promptly, rapidly, thus regrowth of leiomyoma was not observed, and caused no significant difference of mean serum E_2 concentration between pretreatment and during treatment. This is not comparable to the others which have demonstrated the complete gonadal suppression occurred at the end of 4 weeks of intranasal buserelin.[6,10] These results may be explained

in part by the difference of compliance of patients in each study. For long acting GnRH-a, E_2 concentration of all cases were decreased to post-menopausal level after 4 weeks of treatment with the reasons as described above.[5,7,8,11]

From this study, the reduction of tumour volume was observed despite the incomplete gonadal suppression. This indicates that the response of leiomyoma to GnRH-a does not necessitate absolutely severe hypoestrogenism and variation of individual sensitivity of leiomyoma that may be explained in part by additional factors which effect tumour growth and genetic factors.

The incidence of vaginal bleeding and adverse symptoms observed in this study were much less than the others.[5,7] This should be the advantage of the drug that all patients can tolerate with no more suffering during treatment. Because of reduction in leiomyoma volume, tumour related symptoms diminished and disappeared at the end of 8 weeks which is comparable to the previous reports.[10,11] This preliminary report demonstrated the efficacy of intranasal buserelin in reduction of uterine leiomyoma volume and alleviation of clinical symptoms in Thai patients. Preoperative GnRH-a administration may improve patient condition before surgery, may facilitate the surgical procedure and diminish blood loss during operation. However, the usefulness and cost-benefit of GnRH-a as a preoperative treatment of uterine leiomyoma should be evaluated further.

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GYNAECOLOGY

Abnormal Menstrual Cycle in Second Year Medical Students at Siriraj Hospital

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ABSTRACT

Objective To determine the effect of psychological stress on the menstrual cycle in second year medical students.

Design Before and after study.

Setting Department of Physiology, Faculty of Medicine Siriraj Hospital.

Subjects Forty-nine volunteers (18 - 21 years old) from second year medical students were studied. Two blood samples were collected from each student, one during the assumed non-stressed (ANS) period and the other during the assumed stressed (AS) period.

Main outcome measures Characteristic of menstrual cycle was recorded. Serum cortisol, prolactin, gonadotropins and progesterone were measured using radioimmunoassay.

Results Abnormal cycles were found in 2 characteristics : (1) irregular cycle comprised 22% of all subjects ; (2) low serum progesterone in the assumed luteal phase, implying anovulation or luteal defect, comprised 62% and 70% of subjects during the ANS and the AS periods respectively. There was no significant difference in the incidence of abnormal cycle between the two periods. No correlation between serum levels of progesterone and cortisol, prolactin or LH : FSH ratio could be demonstrated.

Conclusion Over 60% of second year medical students at Siriraj Hospital had abnormal menstrual cycles. We could not demonstrate the correlation between this high incidence and the level of stress hormone, i.e. cortisol.

Key words : abnormal menstrual cycle, medical students, psychological stress

Medical school is a stressful environment in which various stressors have been identified.[1] Female medical students are reported to have higher level of stress than male colleagues.[2] Mental stress, which can affect academic performance and health of medical students,[2] produces numerous alterations in psychoneuroendocrine responses which consequently affect reproductive function.[3] Abnormal female reproductive function is usually expressed as an abnormal menstrual cycle, for example abnormal luteal phase, anovulation (with or without cycle irregularity) or amenorrhoea.[4]

Due to the curriculum of the Faculty of Medicine Siriraj Hospital, during the second year which is the first of two preclinical years, medical students have to attend three major subjects, i.e. Anatomy, Physiology and Biochemistry, and also other minor subjects. Since these subjects are entirely different from those of first premedical year, the students have to adjust themselves so much, hence, induce them some level of stress.

This study aims to determine : (1) the incidence of abnormal menstrual cycle in second year medical students whom are assumed to have high level of stress and (2) the correlation between serum levels of progesterone in the assumed luteal phase and some other hormones that are affected by stress and have putative effects on reproductive functions.

Materials and Methods

Subjects were second year medical students attending Physiology class at the Faculty of Medicine Siriraj Hospital, Mahidol University.

Forty-nine female volunteers, aged 18 - 21 years, were asked to answer the questionnaire enquiring about their health status and menstrual history. All subjects were healthy and within an acceptable range of body mass index (16.03 - 25.80 kg/m^2).

Two blood samples were collected from each volunteer. The first sample was taken during the assumed non-stress (ANS) period at the beginning of the second semester when they commenced their Physiology class. The second sample was taken during the assumed stress (AS) period within a few days before the Physiology examination.

Ten millilitres of blood were drawn between 8.00-9.00 a.m. from each subject and collected in a non-heparinized glass tube. Serum was separated and frozen at -20 °C until hormonal assay was performed. Serum cortisol, prolactin, progesterone and gonadotropins, i.e. luteinizing hormone and follicle stimulating hormone (LH and FSH) were measured using radioimmunoassay techniques (WHO protocol).[5]

Day of menstrual period, especially the assumed luteal phase, was estimated from last menstrual period (LMP) on 2 assumptions. One is that a woman who has a cyclic, spontaneous and predictable menstruation is strong evidence for recurrent ovulation[4] and the other is that adequate luteal phase lasts at least 11 days (range 11 - 17 days).[6]

Abnormal menstrual cycle was defined as an irregular cycle or a regular cycle with low serum progesterone in the assumed luteal phase (less than 9.8 nmol/L) within the day between 4 and 11 days before menstruation.[7-9]

The results were tabulated as mean ± SD and percent. Paired t-test and Chi-square test were used to compare values in the ANS with those in the AS period. Linear regression analysis was used to determine the correlation between serum progesterone and other hormones. Statistical significance was accepted at P value of less than 0.05.

Results

From 49 subjects, 11 students (22%) had an irregular menstrual cycle while another 38 students had a regular cycle of every 28.32 ± 3.25 days (range 21 - 35 days).

Among 38 students who reported a regular cycle, 21 students in the ANS and 10 students in the AS period were expected to be in the luteal phase : 62% of the former and 70% of the latter had serum progesterone levels in the assumed luteal phase less than 9.8 nmol/L (Table 1). No significant difference in the incidence of students having low luteal progesterone levels between the ANS and the AS periods was found (P = 0.725).

There was no significant difference between serum cortisol levels during the ANS period (788 ± 216 nmol/L) and the AS period (800 ± 228 nmol/L) (P = 0.240) The data on hormone profile in both periods were grouped together when linear regression between serum progesterone and other hormones were analysed. No correlation between serum levels of progesterone and cortisol, prolactin or LH:FSH ratio could be demonstrated (Fig. 1).

Discussion

There are several methods for evaluation of female reproductive functions. In this study, serum

Table 1. Serum progesterone in the assumed luteal phase of the students during the assumed non-stressed (ANS) and the assumed stressed (AS) periods

Serum progesterone (nmol/L)		Number of students (%)	
		ANS	AS
low	(< 9.8)	13 (62)	7 (70)
normal	(≥ 9.8)	8 (38)	3 (30)
total		21 (100)	10 (100)

p = 0.725 (Chi-square test)

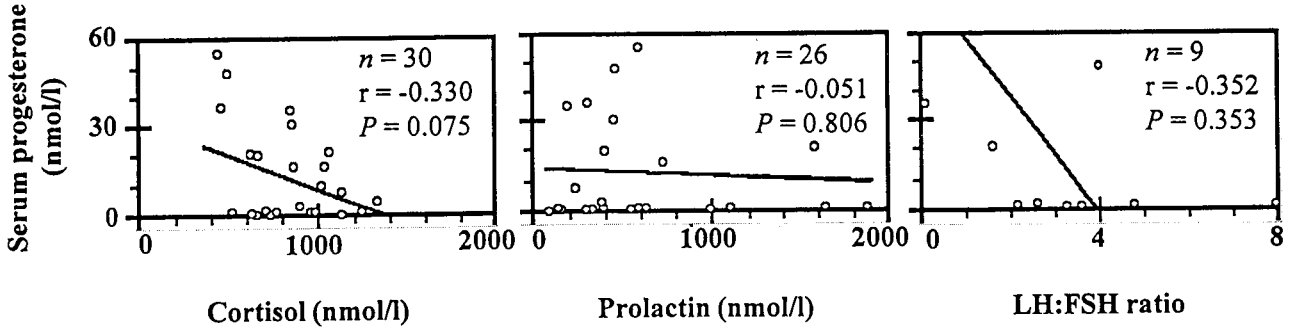

Fig. 1. Correlation between serum progesterone in the assumed luteal phase and cortisol, prolactin and LH : FSH ratio.

progesterone in the assumed luteal phase was used because it is difficult to interpret other parameters or hormones in a cross-sectional study like this.

In this study, 22% of subjects had an irregular menstrual cycle which implied abnormality in reproductive function.[4] Furthermore, over 60% of students who reported previously regular cycles had abnormal low serum progesterone in the assumed luteal phase and therefore should be considered as having abnormal cycles, either anovulation or luteal defect. There were evidences that cyclic bleeding found in an anovulatory cycle was clinically indistinguishable from normal ovulatory menstruation[10] but this proposition is still debated.[4]

The incidence of luteal defect and/or anovulation in the general population varies with the groups studied and the diagnostic measures.[10-12] Our results indicated that this incidence in second year medical students was high. An abnormal cycle in these girls may be associated with chronic stress that concurrently induced persistently high serum cortisol. The instability of the hypothalamic-pituitary-gonadal axis, the function of which still does not reach maximum in this late adolescent age group,[11] was another possibility. However, a girl at this age should have ovulatory cycle in 60-80% of menstrual cycles.[13]

Stress produces considerable alteration in psychoneuroendocrine responses which in turn affect reproductive function.[3,14] The increased corticotropin-releasing hormone (CRH) associated with increased activity of central opioid peptide and serotoninergic pathway can interrupt reproductive function[15] via disturbance of gonadotropin releasing hormone (GnRH) pulsation[14,16] which in turn affects LH secretion. In addition, concurrently elevated CRH and opioid peptide cause changes in both cortisol and prolactin levels which also affect reproductive function. Other than these hormones and peptides, central neuroregulation of the secretion of multiple pituitary hormones, for example thyroid stimulating hormone, are also disturbed.[17] They also have effects on reproductive function.

In the present study, there was a tendency to have lower serum progesterone levels with higher serum cortisol levels. However, no significant correlation between serum progesterone levels and cortisol or prolactin levels was observed.

The LH : FSH ratio is considered abnormal if it is higher than 3 except at the time of ovulation. An abnormal LH:FSH ratio is usually found in the condition with chronic anovulation.[6] Nevertheless, this study could not confirm any correlation between low serum progesterone and a high LH : FSH ratio.

From this study the correlation between an abnormal menstrual cycle and psychological stress could not be proven since the incidence of students showing abnormal menstrual cycle during the ANS and the AS periods were not significantly different. This may be because of equality in the levels of stress between these two periods, as indicated by comparable serum cortisol levels in both periods.[18] High cortisol levels in the ANS period may arise from stressors other than examination. Persistently high cortisol level in the AS period may refer to an inability of subjects to cope with stress[19,20] or their inability to increase cortisol level in response to additional stress.

In conclusion, this result suggested a high incidence of abnormal menstrual cycles in second year medical students at Siriraj Hospital. Although no correlation between low serum progesterone and other hormones responding to stress could be demonstrated, we were unable to discount the

possibility that anovulatory cycle in these students may be associated with high cortisol, prolactin or abnormal LH : FSH secretion. Since second year medical students at Siriraj Hospital seemed to fall under a prolonged or chronic stress (as suggested by persistently high cortisol level), other groups of students who have fluctuated level of stress might be a better subject to study.

Acknowledgement

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GYNAECOLOGY

A Survey Contraceptive Practice in Thai Female HIV-1 Positive Prostitutes

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ABSTRACT

Objective To survey the contraceptive use and characteristics of HIV-1 infected prostitute.

Design Cross-sectional descriptive study.

Subjects and methods A cross-sectional survey of contraceptive practice in Thai female HIV-1 prostitutes was done, 158 HIV-1 infected prostitutes from Bangkok, Khon Kaen and Lampang were recruited to study. The study was conducted from 1st October 1993 to 30th September 1994.

Results From the study, it was found that average age of prostitutes with HIV-1 +ve was 23.7 ± 5.5 years old and mostly had primary school education. Most of them had duration of work more than 1 year. The contraceptive prevalence rate was 72.7%. The most contraceptive method use was oral pill and the least was subdermal implant. Only 3.8% of prostitutes' regular partners or husbands used condom regularly for contraception.

Conclusion Most of HIV-1 infected prostitutes had contraception. However, a few prostitutes used condom regularly with their partners or husbands. To educate and encourage use of condom should be an effective method to prevent and control HIV infection.

Key words : contraceptive, HIV-1, prostitutes

HIV infection among Thai female prostitutes has been increased since 1985.[1] National median provincial rates for brothel-based prostitutes increased steadily from 3.5% in June 1989 to 15% in June 1991.[1] To date, contraceptive practice in this group had few reports. Because

specific contraceptive methods may increase or decrease prostitutes' susceptibility to HIV infection, given exposure, or her infectivity to her partner if she is already infected with HIV, family planning and HIV control are interrelated.[2] Knowing the contraceptive method use among these prostitutes are benefit for AIDS control and family planning programme. The objectives of this study were to survey the contraceptive use and characteristics of HIV-1 infected prostitutes.

Materials and Methods

1. Study design

This study was descriptive study, through the interview of 158 HIV-1 infected prostitutes, receiving the health check up at Bangrak Venereal Disease Hospital, Bangkok, Venereal Disease Control Centre in Khon Kaen province and Venereal Disease Clinic of Lampang Provincial Health Office, Lampang province, by using the questionnaires which were tested already.

2. The interviews were conducted by the authors and nurses at clinic who had previously attended the workshop in which the author explained the purposes of the study and the meaning of questionnaires.

3. Population

The population of this study were the HIV-1 infected prostitutes who had already confirmed with Western Blot. All of them still conducted the job and willing to participate in the study as well as to answer the questionnaires according to the fact after informing by interviewers. Of 158 prostitutes, 40 were from Bangkok, 42 were from Khon Kaen province and 76 were from Lampang province.

4. The period of study

This study was started from 1st October 1993 to 30th September 1994, total period of one year.

5. Data analysis

All data were collected, coded and analysed by the authors. SPSS/PC+ and CIA statistical package programme were used to analyse the data. Statistical values were percent, mean, standard deviation and 95% confidence interval.

6. Variables

Variables in this study were composed of age, educational level, starting age of entering prostitutes, duration of being prostitutes, number of children, workplace, rate of service charge, history of induced abortion, number of clients, sexual intercourse during menstruation, contraceptive prevalence rate and contraceptive methods.

Results

The majority of prostitutes in this study were aged between 20 and 29 years (Table 1). The mean age was 23.7 years with standard deviation 5.5 years, range 16 to 47 years. Most of them had low educational level, 91.8% reached primary school level or lower. Only 0.6% completed vocational school (Table 1). The minimum starting age of entering prostitutes was 12 years old while the maximum starting age was 40 years old. The average age of starting was 19.4 ± 5.0 years old. The duration of being prostitutes varied from 1 month to 15 years. Most of prostitutes had no children. Only 3.8% had 3 children, 83.5% of prostitutes had no history of induced abortion. However, the remaining had frequency of induced abortion ranged from 1 to 5 occasions (Table 1). Considering the workplace, the prostitutes in this study came from a wide variety of workplace. Most worked in brothels. Only 7% worked in massage parlour while the remaining worked in coffee shop, bar, pub and others (Table 2). Rate of

Table 1. Characteristics of HIV-1 positive prostitutes

Characteristics	Number	Percent	95% CI
- Age (year)			
15 - 19	40	25.4	18.5 - 32.1
20 - 24	61	38.6	31.0 - 46.2
25 - 29	36	22.8	16.2 - 29.3
30 - 34	16	10.1	5.4 - 14.8
35 - 39	1	0.6	0.02 - 3.5
above 40	4	2.5	0.7 - 6.4
- Education			
Illiteracy	17	10.8	5.9 - 15.6
Primary school	128	81.0	74.9 - 87.1
Secondary school	12	7.6	4.0 - 12.9
Vocational school	1	0.6	0.02 - 3.5
- Starting age of being prostitute (years)			
Below 14	13	8.2	4.5 - 13.7
15 - 19	88	55.7	48.0 - 63.4
20 - 24	35	22.2	15.7 - 28.6
25 - 29	12	7.6	64.0 - 12.9
above 30	10	6.3	3.1 - 11.3
- Duration of being prostitute (year)			
Less than 1	9	5.7	2.6 - 10.5
1 - 2	52	32.9	25.6 40.2
3 - 4	38	24.1	17.4 - 30.7
More than 4	59	37.3	29.8 - 44.9
- Number of children			
None	98	62.0	54.5 - 69.6
1	43	27.2	20.3 - 34.2
2	11	7.0	3.5 - 12.1
3	6	3.8	1.4 - 8.1
- Number of induced abortion			
None	132	83.5	77.8 - 89.3
1	17	10.8	5.9 - 1.6
2	5	3.2	1.0 - 7.2
3	3	1.9	0.4 - 5.5
4	1	0.6	0.02 - 3.5

Table 2. Workplace

Workplace	Number	Percent	95% CI
Brothel	71	44.9	37.2 - 52.7
Coffee shop, bar, pub	45	28.5	21.4 - 35.5
Massage parlour	11	7.0	3.5 - 12.1
Others	31	19.6	13.4 - 25.8
Total	158	100.0	

Table 3. Rate of service charge

Rate of service charge/Time (Baht)	Number	Percent	95% CI
Below 100	67	42.4	34.7 - 50.1
101 - 200	30	19.0	12.9 - 25.1
201 - 300	9	5.7	2.6 - 10.5
301 - 400	1	0.6	0.02 - 3.5
401 - 500	22	13.9	8.5 - 19.3
501 - 600	5	3.2	1.0 - 7.2
601 - 700	10	6.4	3.1 - 11.3
701 - 800	1	0.6	0.02 - 3.5
801 - 900	1	0.6	0.02 - 3.5
901 - 1,000	9	5.7	2.6 - 10.5
Above 1,000	3	1.9	0.4 - 5.5
Total	158	100.0	

Table 4. Number of clients per week

Number of clients/week	Number	Percent	95% CI
1 - 20	92	58.2	50.5 - 65.9
21 - 40	51	32.3	25.0 - 39.6
41 - 60	11	7.0	3.5 - 12.1
61 - 80	3	1.9	0.4 - 5.5
above 80	1	0.6	0.02 - 3.5
Total	158	100.0	

Table 5. Sexual intercourse during menstruation

Frequency of sexual intercourse	Number	Percent	95% CI
None	122	77.2	70.7 - 83.8
Decrease	22	13.9	8.5 - 19.3
Regular	14	8.9	4.9 - 14.4
Total	158	100.0	

Table 6. Contraceptive method of prostitutes

Contraceptive method	Number	Percent	95% CI
Oral pill	73	46.2	38.4 - 54.0
Injection	26	16.5	10.7 - 22.2
Intrauterine device	2	1.3	0.2 - 4.5
Condom	6	3.8	1.4 - 8.1
Tubal ligation	7	4.4	1.8 - 8.9
Subdermal implant	1	0.6	0.02 - 3.5
None	43	27.2	20.3 - 34.2
Total	158	100.0	

service charge of prostitutes in this study varied from 50 Baht to 1,500 Baht (25 Baht approximately = 1 US$). Most of them received service charge less than 100 Baht or about 4 US$ (Table 3). The reported number of clients in the week prior to interview ranged from 1 to 84 (Table 4), 77.2% of these prostitutes denied to have sexual intercourse during menstruation. Only 8.9% had regular sexual activity (Table 5). The contraceptive prevalence rate among these group of prostitutes were 72.8%. The oral contraceptive pill was the most favoured form of contraception for 46.2% of them. Only 3.8% of prostitutes relied on condom without spermicide or other contraceptive method with their regular partners or husbands (Table 6).

Discussion

In Thailand, prostitutes are now a major conduit for transmission of HIV infection. HIV prevalence rates in Thai prostitutes are high and they are the source of spreading HIV infection. This study revealed that HIV-1 infected prostitutes were young with low socioeconomic status. These were the common characteristics of prostitutes.[1,3] However the starting age of being prostitutes at age was below 20 years old. The previous studies also showed the same result.[1,3,4] Most of the prostitutes in this study

had duration of work more than 2 years. So, during the period of working, they could spread HIV through their clients. It would be very difficult to control HIV infection among these prostitutes if they still worked and did not practice safe sex. Encouraging the use of condom was a measure to control HIV infection.[1] Most of HIV infected prostitutes in this study worked in brothels and low service charge that cater for urban and rural low income male labourers and agriculture workers who paid low price for sex services.[1] These clients belonged to low socioeconomic and poor hygiene group. Most of them had little knowledge about AIDS and did not prefer to use condom. So, HIV infection could spread to these clients easily. Approximately 58% of the prostitutes serviced between 1-20 clients per week which was similar to previous study.[3,5,6] There were some prostitutes who still practiced sexual intercourse during menstruation which could put them at risk of genital tract infection and AIDS.[7]

Focusing on contraception, it revealed that most of HIV infected prostitutes practiced contraception. The contraceptive prevalence rate was 72.8% which was higher than that of the rest of the country during the same period which was only 61.7%.[8] This showed that the HIV infected prostitutes in the study had an interest in birth control. However, specific contraceptive methods may increase or decrease HIV susceptibility and infectivity.[2] So, the usage of appropriate contraceptive methods could prevent HIV infection.

In this study, there were 46.2% of prostitutes used oral hormonal contraceptive pill. The use of oral hormonal contraceptive is associated with an increased risk for HIV acquisition remains controversial.[2] Some studies reported increased risk for HIV infection among oral contraceptive pill users because of cervical ectopion[9] and irregular bleeding.[2] But other studies didn't find this association.[10,11] So, there is no conclusion about association between oral contraceptive pill and HIV infection. Considering the injectable hormone, there were 16.5% of prostitutes in this study who used this method. Menstrual irregularities were common symptom among injectable users which could theoretically increased risk of HIV transmission.[2] Medroxyprogesterone could also cause enhanced vulnerability of the vaginal epithelium through thinning of this tissue and thus facilitate transmission of HIV through superficial lesions.[2] Using non-sterile needle and syringe were also the risk factors of HIV infection. So, injectable hormone should not be recommended for these prostitutes. Intrauterine devices also increase risk of HIV infection and pelvic inflammatory disease.[11] The prostitutes who used intrauterine device should change the contraceptive methods to reduce risk of HIV and pelvic inflammatory disease. The use of condom can prevent AIDS and sexual transmitted diseases as well as contraception.[12,13] Nevertheless, there were only 3.8% of the prostitutes' regular partners or husbands who used condom regularly for contraception. This was different from the developed country where the prostitutes used condom regularly up to 69%.[3] The use of condom is a result of the outbreak of AIDS.[14] Unfortunately, the questionnaires of this study asked only the condom use of their regular partners as contraception. So, there might be some prostitutes who use other contraception with condom to prevent sexually transmitted disease. Further study should be done to explore the condom use for this purpose.

In summary, most of HIV infected prostitutes used contraceptive methods. However, some

contraceptive practice may increase or decrease risk of HIV infection. Encouraging the use of appropriate contraception such as condom should be benefit for these prostitutes in prevention of AIDS and birth control.

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GYNAECOLOGY

Cervical Chlamydia trachomatis Infection Related Mucopurulent Cervicitis (MPC) among Commercial Sex Workers Attending a Private Sexually Transmitted Diseases (STD) Clinic

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ABSTRACT

Objective To study the prevalence of cervical Chlamydia trachomatis infection among masseuses who are female commercial sex workers (CSWs), and the association between C. trachomatis and mucopurulent cervicitis (MPC).

Design Cross-sectional study.

Setting A private Sexually Transmitted Clinic (STD) affiliated with Hat Yai STD unit.

Subjects The study group was 125 masseuses work at a modern massage parlor in Hat Yai who regularly visited the clinic to have routine check-up for common STD every week.

Main outcome measures Chlamydial isolation, and PMN criteria of endocervical smear stain.

Results The prevalence of cervical C. trachomatis infection is 12 in 125 cases (9.6%). Most (11 in 12 cases) of cervical C. trachomatis infection (91.6%) had no abnormal vaginal discharge (AVD). Half (6 in 12 cases) of cervical C.trachomatis infection had associated with MPC. According to the PMN criteria of 10 or more, cervical C.trachomatis infection were found 6 in 91cases (6.5%) of non-MPC, and 6 in 34 cases (17.6%) of MPC. In comparison with the PMN criteria of 30 or more, cervical C.trachomatis infection were found 7 in 87 cases (8.0%) of non-MPC, and 5 in 38 cases (13.2%) of MPC. There were no statistical difference ($P > 0.5$) between two different PMN criteria and cervical C. trachomatis infection or MPC.

Conclusion The AVD is only suggestive information, but PMN criteria either ≥10 or ≥ 30 is found to be confirmative diagnosis of MPC, but no difference is associated with positive C. trachomatis.

Key words : chlamydial infection, mucopurulent cervicitis, commercial sex workers

Chlamydia trachomatis is among the most prevalent sexually transmitted diseases (STD) and has been shown to be an important cause of mucopurulent cervicitis (MPC), urethritis and salpingitis in women.[1-4] Moreover, it has been shown to be associated with infertility in women,[1-5] and with complications of pregnancy, such as premature rupture of membrane, premature delivery and post-partum endometritis and it is probably the most common causative agent of ophthalmia neonatorum and accounts for many pneumonias in infant.[1-3,6-9] C. trachomatis can be recovered from the cervix in 5 to 35% of sexually active women, depending on the characteristic of the population.[1,10-13] Infection of the cervix is the most common genital infection in women and approximately 50% of these infections are asymptomatic or cause mild or non-specific symptoms and signs. MPC is seen with both N. gonorrhoeae and C. trachomatis with the latter accounting for 60% of cases.[4]

In addition to vaginal discharge, the patient may present with history of postcoital vaginal spotting. On examination, ectopy or eversion of the squamo-columnar junctions is frequently observed and these findings are associated with greater number of inclusions. The cervix is friable, bleeds easily with placement of speculum or sampling of glandular epithelium.[14-16] The term MPC thus can be broadly defined as indicating the presence of endocervical PMN leukocyte exudate, as manifested either by visible mucopurulent (the colour should be noted in comparison with the white colour of the swab, where as the characteristic of the endocervical secretion was categorized into clear, cloudy, and mucopurulent), or by the presence of ≥10 PMN leukocytes per X 1,000 field when examine at least 5 separate areas on a smear-stained specimen of endocervical mucus which has been properly collected to avoid contamination with vaginal cells.[4] We proposed another PMN criteria by the presence of ≥ 30 PMN leukocytes per X 1,000 field when examine at least one separate area on a smear-stained.

The fact that many chlamydial infections elude clinical diagnosis has directly contributed to their increasing incidence and public health importance.[17] We undertook the present study among masseuses work at a modern massage parlor in Hat Yai who regularly visit a private STD clinic to have routine check-up of common STD every week for identification the prevalence of cervical C. trachomatis by using culture method, and their association with MPC.

Materials and Methods

Patient population : The study population consisted of 125 consecutive masseuses attending a private STD clinic affiliated with Hat Yai STD who regularly visit the clinic to have routine check-up for common STD every week in January 1995. The sex workers were excluded as those who had taken antibiotics within the previous two weeks, or positive gonococcal isolation.

Clinical and microscopic evaluation : Each patient was interviewed concerning clinical and sexual history. Information was obtained on patient age, marital status, condom use for prevention of STD, history of AVD, current contraception practices, and exposure to antibiotics in the previous two weeks.

After the ectocervix was wiped clean with a large cotton swab, endocervical mucus was collected on a white-tipped swab, with care taken to avoid contamination by the vaginal secretions. The endocervical culture for C. trachomatis was performed with the use of a cotton-tipped plastic swab which was immediately placed in sucrose-phosphate transport medium on wet ice.

Subsequent to the culturing, another swab was rolled onto a 1 - 2 square centimetres area on a microscopic slide. The smear was heat dry and stained with methylene blue.

Oil was added, and slide was scanned at a magnification of 100 to evaluate the presence and amount of endocervical mucus, to look for squamous cells, and to identify area of mucus that appear to contain inflammatory cell. Most often, polymorphonuclear neutrophil (PMN) leukocytes were distributed uniformly in endocervical mucus, but in cases which they were distributed in a patchy fashion, representative areas containing the densest concentration of such leukocytes were selected. The number of PMN leukocytes per microscopic field at a magnification of 1,000 in 5 nonadjacent fields was then established with use of oil lens.

The presence of ≥ 10 PMN leukocytes per X 1,000 field in mucus supports the diagnosis of MPC, unless heavy contamination by vaginal epithelial cells (e.g. > 100 squamous cells per slide) and vaginal flora (e.g. > 100 bacteria per X 1,000 field overlying endocervical mucus) suggest that the PMN leukocytes may have origin in the vagina rather than in the endocervix. The presence of ≥ 30 PMN leukocytes per X 1,000 field at least one area in the smear also diagnosed as MPC. The demonstration of intracellular diplococci at least three pairs or more is strongly suggestive for gonorrhea.

Laboratory methods : Specimens for isolation of C. trachomatis were stored in the sucrose-phosphate transport media (0.2M) at -70° C before inoculation onto cycloheximide-treated McCoy cells in shell vial. Growth of C. trachomatis was detected with fluorescein-labeled monoclonal antibody (IMAGEN™ Chlamydia ; DAKO Diagnostic Ltd., Denmark) at 48 hours after incubation.

Results

The mean age of the 125 masseuses was 25.10 ± 6.16 years, the range varies from 18 - 45, and about two-third (65.6%) were nulliparous. The most predominant method of contraception was pills (88.8%), followed by DMPA (8.0%).

Nearly all (124 in 125 cases) of them (99.2%) used condoms every time when they had sexual intercourse with the clients in order to prevent STD. Among these, 12 in 125 cases (9.6%) were culture positive for C. trachomatis and diagnosed as cervical C. trachomatis infection. Half (6 in 12 cases) of cervical C. trachomatis infection (50.0%) had associated with mucopurulent cervicitis (MPC). There was only one woman who used condoms occasionally, and her endocervical culture was negative for C. trachomatis. With regard to AVD, 115 in 125 cases (92.0%) had no abnormal vaginal discharge. The characteristic of endocervical secretion was determined ; 6 in 125 cases (4.8%) were mucopurulent discharge (all were C. trachomatis negative), 8 in 125 cases (6.4%) were cloudy (only one case was C. trachomatis positive), and 111 in 125 (88.8%) were clear (11 cases were C. trachomatis positive).

Most (11 in 12 cases) of cervical C. trachomatis infection (91.6%) had no AVD. There were no statistical difference (P = 0.649) between the abnormal vaginal and cervical C. trachomatis infection. The visible mucopus did not relate with cervical C. trachomatis infection.

Table 1 shows the correlation between cervical C.trachomatis infection and MPC. According to the PMN criteria (10 or more) for clinical diagnosis, MPC were found 34 in 125 cases (27.2%). Among these, 6 in 34 cases (17.6%) were MPC with chlamydiae-positive form, and 28 in 34 cases (82.4%) were MPC with

chlamydiae-negative form. Cervical C. trachomatis infection were found 6 in 91 cases (6.5%) of non-MPC, whereas 6 in 34 cases (17.6%) of MPC in the group of PMN criteria of 10 or more (P = 0.127).

In comparison with the PMN criteria (30 or more), MPC were found 38 in 125 cases (30.4%). Among these, 5 in 38 cases (13.2%) were MPC with chlamydiae-positive form, and 33 in 38 cases (86.8%) were MPC with chlamydiae-negative form. Cervical C. trachomatis infection were found 7 in 87 cases (8.0%) of non-MPC, whereas 5 in 38 cases (13.2%) of MPC in the group of PMN criteria of 30 or more (P = 0.573).

Most of MPC are chlamydiae-negative form. Among the two PMN criteria, there were no statistical difference (P > 0.5) between each PMN criteria and cervical C. trachomatis infection or MPC.

Discussion

Cervical C.trachomatis infection in women is important not only because most of the infected women are asymptomatic but also because the consequences can be serious. Among women with urogenital chlamydial infection, an estimated 10% can result in acute salpingitis. The reported prevalence of genital infection varies from 5 to 35% depending on the study population. In this study the prevalence of C. trachomatis infection is rather low compared to other studies even though the study population is a high risk group. In comparison, our unpublished data showed the prevalence of C. trachomatis among pregnant women about 5%. This can be explained by the high rate of condom usage among the masseuses who are influenced by the wide-spread campaign for prevention of HIV. It is generally known that contraceptive methods have significant impact on the acquisition of the sexually transmitted pathogen. Barrier methods are highly effective in preventing the transmission of bacteria and virus during sexual intercourse.

The AVD and the characteristic of the endocervical discharge are not related to the culture positive of chlamydiae neither does the number of PMN in the endocervical gram stain. This study showed no statistical difference between each PMN criteria (10 or more, and 30 or more) and cervical C.trachomatis infection or

Table 1. Correlation between cervical C.trachomatis infection and MPC

	No. of patient(%) N = 125	Culture positive for Chlamydiae (%)	P value
Endocervical secretion			
mucopurulent	6 (4.8)	-	
cloudy	8 (6.4)	1/8 (12.5)	
clear	111 (88.8)	11/111 (9.9)	
PMN criteria of 10 or more			
PMN < 10	91 (72.8)	6/91 (6.5)	
PMN ≥ 10	34 (27.2)	6/34 (17.6)	0.127
PMN criteria of 30 or more			
PMN < 30	87 (69.6)	7/87 (8.0)	
PMN ≥ 30	38 (30.4)	5/38 (13.2)	0.573

MPC. Thus, we suggested that the term of visible mucopus will be used to refer to yellow endocervical discharge, and the term of microscopic mucopus will be used to refer to the presence of ≥ 10 PMN leukocytes per X 1,000 field when examine at least 5 separate area or the presence of ≥ 30 PMN leukocytes per X 1,000 field when examine at least one separate area on a stained smear.

In general practice, the women who have the symptoms of AVD, and found to get along with the PMN criteria of confirmation (either ≥ 10 or ≥ 30) should be diagnosed as MPC. The treatment then should be prescribed according to whether it is chlamydiae-positive or chlamydiae-negative form.[18] The characteristic colour of endocervical discharge is not associated with number of PMN found in stained smear nor is it associated with chlamydial infection. So, the clinical diagnosis of MPC can not depend on the mucopurulent endocervical secretion or PMN criteria alone. More strong and alternative criteria of MPC can be referred to the combination between visible mucopus and microscopic mucopus as the clinical diagnosis.

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REPRODUCTIVE SCIENCE

A Prospective Randomized Trial Comparing Urinary Luteinizing Hormone and Basal Body Temperature Graphs for Timed Sexual Intercourse in Unexplained Infertility

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ABSTRACT

Objective To investigate the influence of simple methods for timed sexual intercourse in natural menstrual cycles between the two groups of patients with unexplained infertility. Group 1 : timed sexual intercourse by conventional basal body temperature graphs. Group 2 : timed sexual intercourse by urinary luteinizing hormone or urine LH home kit.

Design A prospective randomized study.

Setting University Hospital.

Subjects A total of 77 couples with unexplained infertility more than 2 years' duration who attended the infertility clinic for the investigation and treatment of infertility.

Main outcome measures Number of conceptions and monthly fecundability rates.

Results Patients in group 1, of the 39 patients with 194 cycles of follow up who timed sexual intercourse using BBT graphs, 12 (30.77%) conceived which gave the monthly fecundability rate of 0.06. In group 2, of the 38 patients with 183 cycles of follow up using urine LH home kit 20 (52.63%) conceived. The monthly fecundability rate was 0.11. The monthly fecundability rates between these two groups were not statistically significant.

Conclusion This prospective randomized study demonstrated using urine LH home kit for timed sexual intercourse had the trend for higher monthly fecundability rate comparing to BBT graphs and it would require a larger sample size to explore a significant difference.

Key words : unexplained infertility, urinary luteinizing hormone, BBT graphs

It is obvious that precise knowledge of the time of ovulation would be of immense value in both promoting and controlling fertility. Ovulation is the key event in the ovarian cycle, and methods for its identification are critical to the physician caring for the infertile couple. Timed sexual intercourse is a frequently prescribed component in the treatment for infertile couples. Timing of insemination is known to be related to pregnancy rate.[1] A variety of methods for predicting ovulation have been described, including conventional basal body temperature (BBT) graphs,[2,3] measurement of serial plasma luteinizing hormone concentration,[4] and high technology ultrasonic imaging of the ovaries from early in the follicular phase.[4,5] Recently, patients performed urine LH immunoassays have gained widespread acceptance for this purpose.[6,7] Several studies have shown these urine LH immunoassays to be simple, rapid and clinically reliable in predicting the time of ovulation.[3,8-11] We have decided to perform a prospective randomized study to analyse the influence of simple methods for timed sexual intercourse in natural cycles between the two groups of patients with unexplained infertility. Group 1 : timed sexual intercourse by conventional basal body temperature graphs. Group 2 : timed sexual intercourse by urinary luteinizing hormone or urine LH home kit.

Materials and Methods

From January to December 1991. A total of 77 couples with unexplained infertility were recruited in this prospective randomized study at the infertility clinic of the Royal Free Hospital. The age range of the female patients was 20-38 years (mean age 33.5). All couples were randomized for timed sexual intercourse in natural menstrual cycles either by urine LH home kit and basal body temperature graphs for six months to compare the monthly fecundability rate between these two groups. Study participants were randomized into one of the two treatment arms by the last digit of the patient's hospital number to determine the choice of treatment. The criteria for those with the diagnosis of unexplained infertility, the patients must meet the following criteria : all couples had infertility of at least 2 years' duration, the women should have normal basic hormone profile, midluteal phase progesterone, laparoscopy with dye insufflation, hysterosalpingogram, serum antisperm antibody and a post coital test and the male partner should have normal semen analysis, negative antisperm antibody and normal hamster egg penetration testing.

BBT graph was measured from day 5 of the menstrual cycle. The patients were instructed to record oral temperature with a basal thermometer every morning on awakening. The temperature charts were interpreted with the nadir as the predictor point of ovulation. Patients using the urine LH home kit (First Response, Tambrands Ltd, Havant, UK) were asked to check their morning urine starting from day 10 of the menstrual cycle. In group 1 timing for sexual intercourse was planned for the estimated day of ovulation based on the women's previous month BBT graphs. In group 2 timing for sexual intercourse was the following day after positive result of urine LH. All patients were asked to bring either their BBT records or LH tests for consultation monthly at onset of menstruation.

Clinical pregnancy will be determined by the appearance of gestational sac (s) on the ultrasound scans at 6-7 weeks' gestation using abdominal or vaginal techniques. Biochemical pregnancy, which means positive urinary hCG will not be included.

Data are presented in number and fecundability rate. Statistical comparisons were performed with Chi-square analysis. P value < 0.05 was defined as statistical significance.

Results

Patients in group 1, of the 39 patients with 194 cycles of follow up who timed sexual intercourse using BBT graphs, 12 (30.77%) conceived which gave the monthly fecundability rate of 0.06. In group 2, of the 38 patients with 183 cycles of follow up using urine LH home kit 20 (52.63%) conceived. The monthly fecundability rate was 0.11. The monthly fecundability rates between these two groups were not statistically significant.

Discussion

The inability to conceive promptly can generate considerable stress in a mariage.[12-14] This anxiety is often exacerbated by advice from physicians regarding ideal coital frequency, technique, and timing of fertile period which is the time supposed to have ovulation. Conventionally, the time of occurrence of ovulation has been estimated from the thermal shift in the BBT. However, temperature records are subjective to a variety of interfering factors, and the BBT alone is not a reliable index for the timing of ovulation. Follicular collapse as visualized by ultrasonography has been claimed to provide the most direct evidence of ovulation but facilities for ultrasound are not always available and the procedure requires daily visit. The urinary LH assay which is a simple, clinically reliable and rapid method will definitely have important potential in fertility regulation both to assist in the timing of natural or artificial insemination and also as an adjunct to natural family planning. Data from several studies clearly suggest that urinary LH assay is an accurate method of predicting ovulation.[3,8-11,15]

Kossoy et al[16] in a retrospective analysis of 120 patients undergoing intracervical insemination with fresh donor semen, found similar fecundability rates in patients using urine LH home kit compared with a control group of patients scheduling insemination by traditional BBT methods. Federman et al[17] recently reported a prospective randomized study of 60 patients undergoing therapeutic donor insemination. They found a higher fecundability rate in patients utilizing LH kits compared with traditional BBT scheduling methods for therapeutic donor inseminations.

Our prospective randomized study of 77 patients to analyse the influence of methods for timed sexual intercourse in natural menstrual cycles in patients with unexplained infertility indicated that 12 out of 39 (30.77%) patients in group 1 who timed sexual intercourse by conventional BBT graphs became pregnant in a total of 194

Table 1. Comparison of number of conceptions and monthly fecundability rate between group 1 and 2

	No.of patients	Cycles of follow up	No. of conceptions	Monthly fecundability
Group 1 (BBT graphs)	39	194	12	0.06
Group 2 (urine LH)	38	183	20	0.11

cycles of follow up for a monthly fecundability rate of 0.06, and 20 out of 38 (52.63%) patients in group 2 who timed sexual intercourse by urinary luteinizing hormone or urine LH home kit became pregnant in a total of 183 cycles of follow up for a monthly fecundability rate of 0.11. Although the differences of monthly fecundability rate were not significant. However, patients in group 2 had the trend for higher monthly fecundability rate which was nearly doubled comparing to group 1. These findings suggest that sufficient advantage may be derived from use of an urine LH home kit to recommend its use as a method of choice for timing sexual intercourse.

In conclusion, this prospective randomized study demonstrated using urine LH home kit for timed sexual intercourse had the trend for higher monthly fecundability rate comparing to conventional BBT graphs and it would require a larger sample size to explore a significant difference.

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CASE REPORT

Uterine Rupture during Labour Induced by Misoprostol

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ABSTRACT

Prostaglandin E_2 has been successfully used for preinduction cervical ripening and labour induction. Recently an alternative prostaglandin E_1 analogue misoprostol is being used instead. It is inexpensive and chemically stable at room temperature. We reported two cases of term pregnancy with uterine rupture using prostaglandin E_1 analogue.

Key words : vaginal misoprostol, uterine rupture, term pregnancy

The preinduction cervical ripening using prostaglandin E_2 (PGE_2, dinoprostone) is generally accepted either in the form of vaginal tablet[1] or intracervical gel.[2] In Ramathibodi Hospital prostaglandin has been used for labour induction with an unfavourable cervix since 1986. Initially prostaglandin E_2 3 mg tablet was crushed and mixed with 3cc of hydroethyl cellulose (K-Y jelly®, Johnson and Johnson) and applied intracervically with good results.[3] Later on the dose of prostaglandin E_2 gel (Prostin E_2®, Upjohn) was reduced to 1.5 mg (half tablet) also with equally good results.[4]

Recently several investigation have described the use of an alternative prostaglandin E_1 analogue misoprostol (Cytotec®, Searle) for preinduction cervical ripening and labour induction.[5-8] Misoprostol is inexpensive, freely available and easy to administer in the vagina. We have previously reported 3 cases of uterine rupture using prostaglandin E_2.[9] We are now reporting two further cases of uterine rupture this time using prostaglandin E_1 analogue, which is a more potent prostaglandin.

Case Report

Case 1. August 1995

A-34-year old gravida 3 para 1 with one spontaneous abortion and a pregnancy terminated at 35 weeks' gestation by caesarean section for severe preeclampsia. The infant weighed 1,800 g now alive and well. This time she was admitted to

the antenatal ward for a repeated caesarean section at 38 weeks' gestation. Throughout her antenatal period, the blood pressure was fluctuate between 130-150 mm Hg systolic and 90-100 mm Hg diastolic. She was diagnosed as having chronic hypertension. During the night of admission, her blood pressure shot up to 170/110 mm Hg and nifedipine 10 mg sublingually was inadvertently ordered. The fetal heart was not detected in the morning and subsequent ultrasound confirmed dead fetus in utero. Since the cervix was unfavourable (Bishop score of 4) misoprostol 100 μg (half tablet) was placed in the vaginal posterior fornix at 7.45 hour. At 17.30 hour spontaneous rupture of membranes occurred and by which time the cervix was 3 cm dilated. The uterine contraction was every 2 minutes 45 seconds lasting 30 seconds. The cervix was fully dilated at 20.15 hour, and a stillborn male infant was delivered by vacuum extraction due to increased blood pressure. The infant weighed 2,810 g.

Severe postpartum haemorrhage occurred immediately after the end of third stage. Examination of the cervix showed a cervical tear right lateral posterior extended into the lower segment. A laparotomy was performed under general anaesthesia, and the tear was found to extend to the insertion of the right-round ligament. The previous lower segment scar was intacted. Subtotal hysterectomy was performed with the repair of cervix. The postoperative period was uneventful.

Case 2. August 1996

A-43-year old gravida 3 para 2 with two previous normal deliveries 14 and 15 years ago. The birthweight was 3,000 and 3,300 g, respectively. The labour was induced at 37 weeks due to pregnancy induced hypertension. Physical examination was normal and on vaginal examination the cervix was found to be unfavourable (Bishop score of 4). In an attempt to ripen the cervix, the patient was given misoprostol 100 μg (half tablet) in the vaginal posterior fornix at 9.00 hour. She was transferred to labour ward at 14.11 hour by which time the cervix was 3 cm dilated, 80% effaced and vertex presentation at station at - 3. The contraction was every 2 minutes 30 seconds with duration of 30-40 seconds. The membranes were ruptured at 14.30 hour. Three hours later the contraction was roughly the same as before and the cervix was 5 cm dilated, 100% effaced with vertex presentation and at station -1. One hour fifteen minutes later the uterine contraction was every 2 minutes 10 seconds with duration of 30 seconds and the fetal heart was 130 beats per minute. Twenty minutes later the patient was found to be in severe hypovolemic shock with blood pressure 70/50 mmHg and pulse 120 beats per minute. The vaginal examination found cervix to be 9 cm dilated with vertex presentation at station -2.

The diagnosis of uterine rupture was made and emergency laparotomy under general anaesthesia revealed an 8 cm rupture in the posterior wall of the uterus, extending from just below the level of the insertion of both round ligaments to the lower segment. The placenta was found to be protruded half way out of the uterus. Stillborn female infant weighed 3,020 g was still inside the uterus. A subtotal hysterectomy was performed. Postoperative period was uneventful.

Discussion

Prostaglandin E is a potent oxytocic agent and is efficient in initiating labour as well as improving the condition of the unfavourable cervix.[1-4] Its use is not without serious adverse

side-effects such as hyperstimulation, fetal distress, and in particular, the risk of uterine rupture.[9] Initially it was thought that the dose used was too high and it was gradually reduced to 0.5 mg (Prepidil, dinoprostone, Upjohn) and still uterine rupture occurred.[10,11] The current available PGE in natural form is very expensive and unstable at room temperature. When the misoprostol was found to be equally if not more effective, its use becomes widespread without knowing the exact dose to use, and being an analogue it is very potent indeed.[5-8] It is certainly less expensive (in Thailand 60 tablets of misoprostol equal to one tablet of Prostin E_2®), and can be kept at room temperature.

In both of these cases there could be some delay in the descend of the fetuses, thus causing the uterine contraction to increase with the build-up of uterine pressure within the uterine cavity leading to uterine rupture. In the first case, the previous scar was intact and vaginal delivery was achieved with vacuum extraction with uterine rupture occurred at the same time. In the second case much the same occurred and the rupture occurred as the cervix was fully dilated causing the head to displace upward. Both cases demonstrated the potency of misoprostol that any slight delay this can occur. Failure to recognize impending uterine rupture made the prevention that more difficult.

Previous reports have suggested that uterine rupture with PGE_2 occurred in patients with prior scarred uterus, or with the use of oxytocin simultaneously or use in multipara. Indeed, as far as we know there is no case of primipara reported with uterine rupture using PGE alone in the unscarred uterus. We strongly recommend that misoprostol be used in primipara only with the lowest dose possible, and oxytocin be used with caution and only absolutely necessary with careful observation for any signs and symptoms of impending uterine rupture. Once detected hyperstimulation of uterine contraction it can be prevented with the use of beta-adrenergic tocolytic drug such as ritodrine or terbutaline.[12,13]

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CASE REPORT

Prolonged Stabilization of Advanced Fallopian Tube Cancer with Leuprolide Acetate

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ABSTRACT

Primary carcinoma of the fallopian tube is an uncommon gynaecologic malignancy with no standard systemic therapy. However, it is usually treated in the same way as epithelial ovarian cancer. In case of chemotherapy failure, hormonal therapy, such as tamoxifen or progesterone, may be used. The GnRH agonists, such as leuprolide acetate, have some activity in advanced platinum refractory ovarian cancer. We presented the case of a 77-year-old woman with stage IV fallopian tube carcinoma. Her disease became resistant to platinum, tamoxifen, and sequentially administered estradiol and megestrol acetate. She was then treated with leuprolide acetate depot 7.5 mg intramuscular injection monthly. The disease was stabilized for 12 months. Therefore, leuprolide acetate may be considered for the treatment of patients with advanced fallopian tube cancer whose disease developed resistance to platinum based chemotherapy.

Key words : fallopian tube cancer, leuprolide

Primary fallopian tube carcinoma is a rare form of gynaecologic malignancy. Therefore, there is limited data regarding the management of advanced disease which failed prior chemotherapy. Some investigators use hormonal therapy in analogy with epithelial ovarian cancer but its

efficacy in fallopian tube cancer remains to be defined. We reported a patient with advanced progressive fallopian tube cancer whose disease was stabilized with leuprolide acetate for one year.

Case Report

A 73-year-old white female who was para 2 with a history of good health most of her life, presented to her physician in May 1993 complaining of a recent onset of increasing fatigue, nausea, and a weight loss of 14 pounds. An ultrasound of the gallbladder and kidneys was unremarkable. The patient was started on omeprazole with a presumptive diagnosis of esophagitis. However, she had no relief of her symptoms. She then underwent a further evaluation, including computed tomographic (CT) scan of the abdomen and pelvis, esophagogastroduodenoscopy, and colonoscopy in June 1993. The CT scan revealed enlarged retroperitoneal lymph nodes, but no other significant finding. The esophagogastroduodeoscopy and colonoscopy did not reveal malignancy but showed colonic polyps. A CT-guided retroperitoneal lymph node fine needle aspiration biopsy was performed. It revealed a metastatic poorly differentiated adenocarcinoma with focal mucin production. The patient was then referred to the University of Texas M.D. Anderson Cancer Centre in August 1993. The physical examination at that time revealed a poorly defined nodularity around the umbilical area, and an enlarged left supraclavicular lymph node sized 1 x 1 cm but no other lymphadenopathy. The pelvic examination and transvaginal ultrasonography did not reveal any pelvic abnormality. The CA125 level was 135 units/ml. A fine needle aspiration of the supraclavicular lymph node confirmed the presence of a metastatic poorly differentiated adenocarcinoma. Therefore, she was considered to have a metastatic adenocarcinoma of an unknown primary site. The possibilities included gastrointestinal and Mullerian (ovarian, peritoneal, fallopian tube) carcinomas. In order to better define the possible options of first line and salvage systemic therapy, an exploratory laparotomy and total abdominal hysterectomy with bilateral salpingo-oophorectomy, omentectomy and tumour reductive surgery were performed in September 1993. The laparotomy revealed a left fallopian tube tumour 3 x 3 cm in size at the fimbria. An infracolic omental mass 7 x 7 cm in size and large retroperitoneal lymphadenopathy, 12 x 8 cm in size, were noted. Interestingly, both ovaries and the uterus were small and appeared atrophic. The para-aortic lymph node mass was too large to be removed. Pathology revealed a high grade papillary serous adenocarcinoma of the left fallopian tube stage IV. (Fig. 1) She was subsequently treated with carboplatin and cyclophosphamide. Her CA125 decreased from 135 to 31.6 units/ml and her periumbilical nodularity was no longer palpable. After seven courses, her retroperitoneal mass and CA125 levels plateaued. Chemotherapy was discontinued in March 1994. Since the laparotomy revealed a

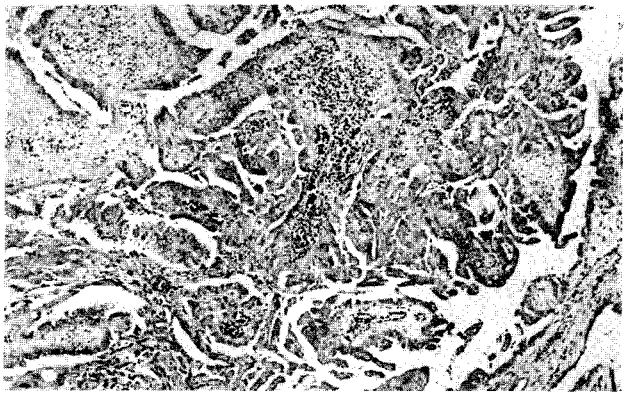

Fig. 1. High grade papillary serous carcinoma of the fallopian tube.

Mullerian carcinoma, we decided to attempt a hormonal anti-cancer therapy as in the treatment of epithelial ovarian malignancies. So her treatment was changed to tamoxifen 40 mg/ day. However, her retroperitoneal mass increased in size in July 94 after three months of the therapy. Therefore, the treatment was changed to sequential estrogen 50 mcg/d on day 1 - 7 and megestrol acetate 40 mg four times a day on day 8-25. This was repeated every 28 days. Two months later in September 1994, her disease progressed as manifested by pelvic pain and enlarging left supraclavicular and para-aortic lymph nodes. We then started treatment with leuprolide acetate depot 7.5 mg intramuscular injection monthly. Her disease was stabilized with no increase in the size of the left supraclavicular and retroperitoneal lymph nodes. Furthermore, she had a decrease in pain. She tolerated this treatment very well with no side effect. However, after twelve months in October 1995, her left supraclavicular lymph node and paraaortic adenopathy, by the CT scan, progressed. Accordingly, the leuprolide acetate therapy was stopped and carboplatin reinduction was initiated.

Discussion

Primary carcinoma of the fallopian tube occurs most frequently in the fifth and sixth decade of life. The classic triad of symptoms consists of a prominent watery vaginal discharge, pelvic pain, and a pelvic mass. However, this triad is seen in fewer than 15% of the patients.[1] Post-menopausal bleeding and abdominal pain are the most common presenting symptoms. This tumour is an uncommon type of gynaecologic malignancy and accounts for only 0.5 - 1.1% of all cancers of the female reproductive tract.[2,3] There is no standard treatment for this cancer. However, it is usually treated in the same way as epithelial ovarian cancer. In advanced cases, cisplatin containing chemotherapy such as CAP (cyclophosphamide, doxorubicin and cisplatin) results in response rates of 21 to 80% with a 5 years survival rate of 13.6 - 51%.[4-7] In case of residual disease after surgery, the median survival is 21months.[7] After failure of chemotherapy, hormonal therapy is used in some institutions.[4,5] In the Roswell Park experience, medroxyprogesterone and tamoxifen were used and resulted in tumour progression after only 2 and 4 months, respectively.[5] However, there is no report of treatment with GnRH agonist. In this patient, after failure with platinum chemotherapy, tamoxifen, and sequentially administered estrogen and megestrol acetate were used based on their activity in epithelial ovarian carcinoma.[8-10] When these failed, leuprolide acetate was started. The latter was chosen based on the evidence of its activity in platinum refractory advanced ovarian cancer.[11,12] In this case, the disease became stable for 12 months. GnRH agonists, such as leuprolide acetate, may be considered for the treatment of patients with advanced fallopian tube cancer.

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REVIEW

Premenstrual Syndrome (PMS)

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ABSTRACT

Premenstrual syndrome (PMS) was first recognized by RT Frank in 1931. However, it was not until 1983 that PMS diagnostic criteria was rather clearly established by The American Psychiatric Association (APA). Various aetiologies have been proposed and recently many studies suggest a deficiency of serotonin in the central serotonergic system. Diagnosis of PMS must be made by prospective recording of the luteal phase related symptoms. Other medical and psychological disorders should be excluded and managed accordingly. Patients with predominantly specific physical symptoms may be treated with specific therapy. Pain-related symptoms should be treated with prostaglandin synthetase inhibitors. Mastalgia may be treated with bromocriptine and significantly weight gain in luteal phase with spironolactone. Psychotropic drugs, especially fluoxetine or alprazolam, may be the first line treatment of severe PMS because of ease of administration and tolerability. Ovulation suppression agents should be preserved for patients who cannot tolerate or do not respond to psychotropic agents. GnRHa with estrogen and progestin add-back may be a good choice for this purpose .

Key words : premenstrual syndrome (PMS), aetiology, diagnostic criteria, treatment

Premenstrual syndrome was first recognized by RT Frank in 1931 to describe a constellation of physical emotional and behavioral symptoms occurring for up to two weeks prior to menses with relief soon after the onset of the menstrual period. Since then, many theories and treatment regimens have been proposed. However, there is no single intervention that will uniformly eradicate premenstrual syndrome and its aetiology remains unknown. There are some main problems associated with the research literature on PMS :

1. Subject selection issues : It was not until 1983 that PMS diagnostic criteria was rather clearly established.[1] Studies prior to 1983 did not incorporate appropriate diagnostic criteria, and therefore suffer from inaccuracy and heterogeneity. Early studies usually admitted subjects who reported premenstrual symptoms and collection of symptoms were retrospective recalls, which are considered to be unreliable.

Moreover, women with concurrent major psychiatric disorders were usually not excluded.[2]

2. Poorly validated and unreliable symptoms measurement techniques : PMS has a large constellation of symptoms (over 100) which almost all are subjective ones. Comparison of treatment results from different studies are very difficult and may be inconsistent.

3. Placebo response rates : Because of high placebo response rate in PMS treatment, any research in treatment of PMS should be a double - blind, placebo-controlled, crossover study. However , the choice of placebo itself can still be a problem. For example, in a placebo-controlled trial of a diuretic or an antidepressant, subjects could probably identify the period of treatment with the active drug because of its adverse effects. If they do, the blind is broken and the study becomes open to expectation bias.[2]

DEFINITION

The simplest definition of the premenstrual syndrome (PMS) is the cyclic appearance of one or more of a large constellation of symptoms (over 100) just prior to menses, occurring to such a degree that lifestyle or work is affected, followed by a period of time entirely free of symptoms. Symptoms usually occur in the last 7 to 10 days of the cycle. The diagnosis is made by prospectively and accurately charting the cycle nature of the symptoms.[1,3]

The American Psychiatric Association (APA) uses the term late luteal phase dysphoric disorder (LLPDD) which appears in the "RESEARCH APPENDIX" of the Diagnostic and Statistical Manual of Mental Disorders, Third edition, Revised (DSM- 3-R). This was published in 1987. These criteria have little modified in 1994 and designated as premenstrual dysphoric disorder (PDD). They are summarized in Table 1.

Table 1. Summary of PDD criteria[4]

A. Symptoms must occur during week before menses and remit a few days after onset of menses
   Five of the following symptoms must be present and at least one must be (1), (2), (3), or (4).
   1. Depressed mood
   2. Anxiety
   3. Lability
   4. Irritability
   5. Decreased interest in usual activities
   6. Difficulty in concentrating
   7. Marked lack of energy
   8. Marked change in appetite, overeating, or food cravings
   9. Hypersomnia or insomnia
   10. Sense of being overwhelmed
   11. Other physical symptoms, e.g., breast tenderness and headaches
B. Symptoms must interfere with work, school, usual activities, relationships
C. Symptoms must not merely be an exacerbation of another disorder
D. Criteria A, B and C must be confirmed by prospective daily ratings for at least two cycles

It should be noted that term PMS and LLPDD or PDD sometimes are used interchangeably. However, acccordingly to the above criteria PDD may be considered a severe form of PMS with predominantly mood symptoms. Some authors also suggested that the aetiology of LLPDD may be different from that of the milder, more somatic forms of PMS and therapeutic strategies will most likely be different.

EPIDEMIOLOGY

Most reproductive-age women appear to experience recurrent premenstrual physical and/or emotional symptoms, although the overall prevalence reported varied between 30 and 90%.[5] In 17 to 40% of women report significant or worrisome problems related to their cycles.[5] Approximately 2.5 - 5% of women of reproductive age meet criteria for PMS.[6] PMS has been reported in all reproductive age groups. No consistent association has been found between PMS and demographic or dietary variables, amount of exercise, level of psychological stress, menstrual cycle characteristics.[5,7,8] The only clinical variable that has been shown to be associated with PMS is mental disorders, both concurrent and lifetime, are high.[9] The strongest association seems to be with lifetime prevalence of affective disorder, especially major depression.[10] Studies also suggested an elevated frequency of postpartum depression up to about 40%.[10] However, Pop VJ et al found that PMS was significantly related to postpartum depression only at the time of the women resumed menstruation (post - puerperium) and suggested that screening on postpartum depression partly involves screening on depressive symptoms related to PMS.[11] Studies in twins suggested increased concordance for heritability of PMS.[12]

AETIOLOGY

Many theories have been proposed to be the aetiology of PMS. These theories are[1] :

Low progesterone levels
High estrogen levels
Falling estrogen levels
Changes in estrogen : progesterone ratios
Increased aldosterone levels
Increased renin - angiotensin activity
Increased adrenal activity
Endogenous endorphin withdrawal
Central changes in catecholamines
Vitamin deficiencies .... etc .

These can be grouped into the following categories :

1. Hypothalamus - pituitary - ovarian axis

The close association of the symptoms of PMS with the luteal phase of the menstrual cycle has led to the postulate that PMS reflects either a physiologic abnormalities or an abnormal to the normal hormonal changes during the luteal phase. Most studies reported no different plasma level of progesterone in PMS patients compared to control.[13,14] Even if some reported lower progesterone level in PMS patients, almost all were the studies before 1983 and the administration of progesterone during the luteal phase of the menstrual cycle in women with PMS has not been more therapeutically effective than placebo.[15,16] Moreover, a significant study by Schmidt et al using the progesterone antagonist (mifepristone) to induce menses or luteolysis suggested that symptoms of PMS could occur even in the absence of the luteal phase. They concluded that endocrine events during the late luteal phase do not directly generate the symptoms of PMS.[17] In another study, Chan et al found that luteal phase administration of low - dose RU 486 does not significantly reduce

the physical or behavioral manifestations of PMS and suggested that progesterone or progesterone receptors are not important mediators of PMS.[18]

Recent studies have reported luteal abnormalities in amplitude and frequency of pulsatile luteinizing hormone secretion.[19] However, the others did not confirm this result.[20] In general most studies have failed to demonstrate differences between women with PMS and control for all hormonal level throughout the menstrual cycle, including estrogen, progesterone, testosterone, follicle - stimulating hormone (FSH), luteinizing hormone (LH), prolactin, and sex hormone binding globulin.[21] However, in anovulatory cycles whether spontaneous or induced by medical or surgical intervention are associated with disappearance of symptoms in PMS.[22,23] This is obvious that hypothalamus - pituitary - ovarian axis must be involved in pathogenesis of PMS .

2. Hypothalamus - pituitary - adrenal axis

Based on the similarity of symptoms of PMS and those observed in major depression, extensive studies have been made to use biochemical markers in endogenous depression as indicators that might be useful in the diagnosis of PMS.[9,24] Patients with primary affective disorders, such as melancholic depression and anorexia nervosa, during episodes of illness frequently have a hyperactive hypothalamus-pituitary - adrenal (HPA) axis. This is characterized by hypersecretion of Corticotropin-releasing hormone (CRH) and a blunted ACTH response to exogenous CRH.[25] Studies have included sampling of urinary free cortisol, plasma cortisol circadian secretory profiles and responses to serial dexamethasone suppression test (DST). Most have found that there were no significant differences in HPA function between the follicular and luteal phases in women with PMS and between those with PMS and control.[21] Recent studies have conflict results. Rabin et al found that basal evening plasma cortisol in PMS was significantly lower than control and the time-integrated response of plasma cortisol to bovine CRH was significantly increased.[25] While Parry BL et al found that plasma cortisol in women with PMS was increased during midcycle phase and DST showed a 62% overall rate nonsuppression, irrespective of menstrual cycle phase.[26] However, this study had no control subject.

3. Thyroid function

It has been known for some time that hypothyroid patients tend to show symptoms of depression. In 1986 it was reported that 94% of women with PMS were found to have thyroid dysfunction, mostly subclinical hypothyroidism which defined by an augmented response to TSH to TRH. They successfully treated all affected women with L - T4 therapy.[27] They expanded their previous work in a second study and it was clear from this study that the subject selection criteria were insufficient.[28] Almost all subsequent studies have not found thyroid dysfunction in PMS.[29] No significant differences were detected in TSH responsiveness to TRH during both follicular and luteal phases.[29] In addition, administration of L-T4 to treat PMS is not better than placebo.[29,30]

4. Nutritional factors

Nutritional supplements have been used widely as treatment of PMS for many years.[2,31] These were based on various proposed aetiologies. However, an excess or deficiency of dietary factors, vitamins and minerals (magnesium, zinc, vitamin A, vitamin E, thiamine, or vitamin B_6) has not been consistently demonstrated in patients with PMS compare with control subjects. Other studies have mixed results ; these includes zinc deficiency, copper

excess, magnesium and zinc deficiency, calcium deficiency or excess, etc.[31,32] It should be noted that administration of vitamins and minerals to treat patients with PMS is not without harmful effect, especially with high dose. For examples, magnesium supplements could interfere with the absorption of calcium and there is a dose-versus-time relationship (larger doses induce symptoms more rapidly) for the development of neurological symptoms in using of megadose of vitamin B_6.[2] At this time the role of vitamins and minerals in PMS, if any, is only speculative and need further clarification.

5. Central changes in catecholamines

In recent years serotonin function was widely studied. It was known that abnormal serotonin metabolism has been linked with certain types of depressive disorders.[33] Blood platelets are utilized as a model of the serotonergic neuron because serotonin uptake, storage, release and metabolism are postulated to be similar in the platelet and in the serotonergic nerve ending. Patients with depression have decreased uptake of serotonin and this decreased uptake may serve as a marker for decreased central serotonergic activity.[34] Rapkin et al found that serotonin levels of premenstrual syndrome subjects were significantly lower during the last ten days of the menstrual cycle.[35] These studies suggest a deficiency in the central serotonergic system. Several treatment trials utilizing pharmacologic agents that release serotonin or block its re-uptake have been shown to be effective for treatment of PMS. However, the serotonergic system is unlikely to be the only system involved in the pathogenesis of PMS.[33]

6. Others

Studies have also examine the effect of menstrual cycle phase on the opiate system, aldosterone activity and multiple other substances.[3] At present no clear cause has been identified with any of these substances and their relationship to the menstrual cycle. In conclusion, even if the aetiology of PMS is still unknown, research related to PMS has advanced in the last few years. Several factors probably contribute to/or interact in the PMS, and it is expected that the aetiology of PMS will eventually be explained by the interaction of gonadal steroids with the central neurotransmitter (probably serotonin), neuroendocrine and circadian systems that influence mood, behavior and cognition.

DIAGNOSIS

According to the definition of PMS and criteria of PDD,[1,4] the pathognomonic for the disorder is the marked fluctuations of symptoms with the menstrual cycle. Symptoms must be confined to the luteal phase. During the time from about the fourth day after the onset of menses until at least cycle day 12, symptoms, if they occur at all, are sporadic and no more frequent than those seen in the general population. Women with cycle that are typically shorter than 26 days in length may have the onset of symptoms slightly earlier than day 12.[6] Women are required to prospectively record their symptoms daily for at least two menstrual cycles. Several prospective rating scales are available.[36] Symptoms associated with PMS include : mood (irritability, mood swings, depression and hostility), somatic (bloating, mastalgia, appetite changes, hot flashes, insomnia, headache, and fatigue), cognitive (confusion and poor concentration) and behavioral (social withdrawal, hyperphagia and arguing). The presence of multiple symptoms is so characteristic that, if the woman has only one symptom, another diagnosis should be considered.[36] Because these symptoms are not unique to PMS, one must

exclude the concomittant medical or psychiatric disorders. The differential diagnosis of cyclic symptoms includes : 1) PMS, 2) PMS plus another disorder, 3) cyclic exacerbation of other disorder, 4) noncyclic other disorder, 5) menstrual - phase symptoms, 6) oral contraceptive use - associated symptoms.[37] The list of "other disorders" is diverse. The most common are psychiatric disorders, especially depression and anxiety. Medical disorders that can present with a luteal - phase pattern include migraine headache, convulsive disorder, irritable bowel syndrome and hypothyroidism.[36] Assessing the symptoms in PMS must also be performed in the absence of any pharmacologic intervention.[6]

Some authors have recognized symptoms of PMS in four patterns, these include : 1) symptoms that gradually increase in severity throughout the luteal phase and abruptly stop with the onset of menses, 2) similar timing of gradually worsening symptoms that continue into the early follicular phase of the next cycle, 3) severe symptoms limited to only a few days in the late luteal phase, 4) two distinct periods of severe symptoms, one around the time of ovulation and a second just before menses.[38]

TREATMENT

Recent advances in the understanding of the pathogenesis of premenstrual syndrome (PMS) have allowed the development of appropriate pharmacological management in PMS. Several well - designed studies with promising results have been conducted that guide the physician's treatment of PMS. Less - proven nonpharmacological modalities (dietary modification, exercise regimens, psychotherapy, etc.) and some medications are quickly supplanted by the use of more - proven medication.[39] Treatment and intervention for treatment of PMS were summarized in Table 2 .

"Placebo response" plays some roles in

Table 2. Summary of modalities in treatment of PMS

Intervention	Method/Dose	Comment	Ref.
1. Non-pharmacologic			
1.1. Diet Modification	e.g. Limit salt intake, eating frequent, small meal with complex carbohydrate, decreased sugar and caffeine, no alcohol, etc.	- can be considered healthful but no evidence of their efficacy in PMS - can gain some control over patient's symptoms - do not clearly indicate a role to treat PMS - need further more well - controlled studies	2, 36
1.2. Relaxation and behavioral therapy	-	- do not clearly indicate a role to treat PMS - need further more well - controlled studies	40
1.3. Light therapy	Bright light (>, = 2,500 lux)	- need further studies	41
1.4. Aerobic exercise	Regular exercise tailored to the	- can be considered healthful but has not been tested directly as a	42

Intervention	Method/Dose	Comment	Ref.
	capabilities of the individual woman	therapy for PMS - fewer premenstrual symptoms (molimina) in several studies	
2. Vitamin and Mineral			
2.1. Vitamin E	alpha-tocopherol 150 - 600 unit/day	- insufficient data to support use - not recommend	43
2.2. Vitamin B_6 (pyridoxine)	50 - 500 mg/day	- weak evidence of its benefit - a dose-versus-time relationship for the development of peripheral neurotoxicity - chronic use of as little as 200 mg carries a risk of neurotoxicity	44 36
2.3. Optivite (high dose multivitamin)	12 tabs/day	- equivocal result - at recommended dose has potentially unsafe levels of vit. B_6 (600 mg) and vit. A - expensive and not recommend	45
2.4. Primrose oil	500 mg tid	- not better than placebo - expensive and not recommend	36, 46
2.5. Calcium	1,000 mg of elemental ion	- improved luteal - phase negative mood, fluid retention and pain in some studies - make sense to general health - can be supplemented by natural sources of calcium	47
3. Drugs			
3.1. Prostaglandin inhibitors			
3.1.1. Mefanamic acid	250-500 mg tid (luteal phase)	- effective in pain - related symptoms	48
3.1.2. Naproxen sodium	550 mg bid (luteal phase)	- effective in pain - related symptoms, especially in menstrual migraine	36
3.2. Bromocriptine	2.5 - 5.0 mg OD (luteal phase)	- useful for the treatment of premenstrual mastalgia - high adverse effects such as headache, fatigue, etc.	36
3.3. Diuretics			
3.3.1. Spironolactone	25 - 50 mg bid (luteal phase)	- research data not convincing - may be useful in patient with luteal phase weight gain > 5 lbs. - generally not recommend	49 36
3.3.2. Thiazides	25 - 50 mg bid (luteal phase)	- risk of diuretic dependence and rebound cyclic edema - not recommend	50
4. Hormone			
4.1. Thyroid	levothyroxine sodium	- has no more effective than placebo	28, 29

Intervention	Method/Dose	Comment	Ref.
hormone	0.13 mg/day -	in treatment of PMS - not recommend	
4.2. Oral contraceptives	monophasic or triphasic pills	- almost all studies focused on premenstrual symptoms, not PMS - a decrease in dysmenorrhea and some molimina was noted but some subjects experienced more depression - Absence of any well - designed, contemporary studies of OCP, especially low dose OCP, use in treatment of PMS - OCP cannot be recommended as PMS treatment at this time	51
4.3. Progesterone	200-800 mg vag.sup. or 300 mg of oral micronized form (luteal phase)	- not better than placebo in almost all studies - should be avoided	15, 16 52
5. Psychotropic Drugs			
5.1. Serotonergic agents			
5.1.1. Antidepressants			
5.1.1.1. Fluoxetine	20 - 60 mg daily (usually 20 mg)	- acts as the selective presynaptic serotonergic reuptake inhibitor - consistently promising results in several well-designed studies for treatment of severe form of PMS or PDD - improvement was found in affective or behavioral than physical symptoms - at low dose (20 mg/day) minimal and tolerable side effects were sexual dysfunction and insomnia - may be considered the first-line treatment for severe PMS or PDD	3, 39 53 - 55
5.1.1.2. Nefazolone	100-600 mg/day	- serotonergic type2 antagonism and serotonin reuptake inhibitor - premenstrual symptoms were improved significantly - needs placebo - controlled studies	56
5.1.1.3. Paroxetine	20-25 mg/day	- selective serotonin reuptake inhibitor - superior to the noradrenaline reuptake inhibitor (maprotiline, another antidepressant) and placebo in severe PMS - needs more studies	57
5.1.2. Fenfluramine	15 mg bid	- stimulates the release of serotonin	58

Intervention	Method/Dose	Comment	Ref.
	(day 14 to day2)	and blocks its reuptakes - significantly decreased carbohydrate consumption and reduced depression scores - needs more studies	
5.1.3. Buspirone	25 mg daily (luteal phase)	- 5HT1A partial agonist - initially suppresses serotonin raphe cell firing, but subsequently potentiate the serotonin system, probably through autoreceptor desensitization - more effective than placebo to treat irritability, fatigue, pain and social functioning	59
5.2. Tricyclic Antidepressants			
5.2.1. Clomipramine	25 - 75 mg/day daily or in luteal phase	- more effective than placebo for PMS or PDD - even at low doses were associated with sedation, dry mouth and constipation	60
5.2.2. Nortriptyline	50 - 125 mg/day	- good therapeutic response in a pilot study, but all subjects noted some adverse effects - needs well controlled studies	61
5.3. Others			
5.3.1. Alprazolam	0.25 mg bid-tid in luteal phase and decreased by 25% daily after initiation menses	- inhibits CNS arousal through potentiation of GABA receptors - short acting benzodiazepine with anxiolytic and antidepressant properties - statistically superior to placebo for specific symptoms such as tension, irritability, anxiety, depression - not effective in one study - may be useful in treatment of severe PMS but must be aware of the adverse effects, tolerance and dependence	16 62 63
5.3.2. Naltrexone	25 mg twice (day 9 to day 18)	- opiate antagonist - associated with significantly fewer symptom than placebo - may be hepatotoxic	2, 64
5.3.3. Clonidine	17 ug/kg/day in 4 divided doses	- effective in reducing psychiatric symptoms, specifically in a subgroup of women with PMS who had cyclic decreases in beta-endorphin levels	65

Intervention	Method/Dose	Comment	Ref.
6. Ovulation Suppression			
6.1. GnRH Agonist	3.75 mg leuprolide IM , monthly or 3.6 mg goserelin SC monthly or 50 ug buserelin SC daily or 400-600ug buserelin intranasal, daily	- suppression of ovulation - effective for both behavioral and physical symptoms in severe PMS or PDD (in most well- controlled studies) - risk of osteoporosis and other unpleasant symptoms of hypoestrogenemia	66, 67
6.2. GnRH a + add back	(6.1) + CEE 625mg D1-25+ MPA10mg D16-25 * start CEE + MPA after GnRHa 2 months	- may extend safety and efficacy of GnRHa for treatment of severe PMS - further research is being studied	68, 69
6.3. Estrogen	- estradiol implant 100 mg + cyclic progestin	- more effective than placebo in severe PMS - some developed PMS-like symptoms during progestin administration - high adverse effects from progestin	70
	- transdermal estradiol 1-200ug twice weekly + cyclic progestin	- more effective than placebo in severe PMS - 100 ug dose is effective and better tolerated - this regimen appears promising	2, 71
6.4. Progestin	MPA 1-30 mg daily or DMPA 150 mg IM every 3 months	- significant improvement in mood and less breast discomfort in one study - generally has not been tested in well- controlled studies - can induce PMS - like symptoms itself	1, 2, 36
6.5. Danazol	200 - 400 mg / day	- superior to placebo in many symptoms (depression, tension, irritability, mastalgia, swelling, etc.) - relatively high side effects and potential long term risks (from both hypoestrogenic and androgenic effects) - needs long term studies of the safety and efficacy)	2, 72
7. Hysterectomy with bilateral ovariectomy	(supplement with low dose estrogen after operation)	- may be indicated for a small, selected group of women who do not respond to conventional therapy	22, 23

PMS in all studies. Some authors recommended to replace this term by "the response to care" or "the response to the doctor" or "the healing response" this is to emphasize that it is a) powerful b) no less than drug actions and c) embedded in every therapeutic transaction.[1] PMS is chronic, very bothersome and varying in severity and symptoms. Physicians should keep all these in mind. Diagnosis of PMS by prospective recording of the luteal phase related symptoms is the very important step in the management of PMS. Other medical and psychological disorders must be excluded and managed accordingly. Meanwhile this is the time to create the doctor-patient relationship. Patients with predominantly specific physical symptoms ay be treated with specific therapy.[1,36] Pain-related symptoms should be treated with prostaglandin synthetase inhibitors, mefanamic acid or naproxen sodium. Mastalgia may be treated with bromocriptine and significantly weight gain in luteal phase may be treated with spironolactone. Psychotropic drugs, especially fluoxetine or alprazolam, may be the first line treatment of severe PMS or PDD because of ease of administration and tolerability.[3] Ovulation suppression agents should be preserved for patients who cannot tolerate or do not respond to psychotropic agents. GnRHa with estrogen and progestin add-back may be a good choice. Hysterectomy and bilateral oophorectomy is rarely indicated and should be done only if all of the following stringent criteria are met.[22,23,36]

1. No response to any therapy except danazol or GnRHa suppression
2. Complete resolution of symptoms while receiving one of these two regimens for a minimum of 4 - 6 months
3. Childbearing completed
4. At least 5 years of menstrual functioning remain and preferably 10 - 15 years.

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GUIDELINES

Committee for the Study of Ethical Aspects of Human Reproduction

International Federation of Gynecology and Obstetrics (FIGO)

ETHICAL GUIDELINES ON THE SALE OF GAMETES AND EMBRYOS

1. The Committee reaffirmed the former statement made in 1993* that the donation of genetic material should be altruistic and free from commercial exploitation. Reasonable compensation for legitimate expenses is appropriate.

2. The Committee noted that some centres offer IVF cycles, sterilization or other medical treatment to women in exchange of oocytes. This is considered to be payment and therefore is unethical.

3. It should also be noted that when payment is involved donors may be tempted to withhold personal information in which, if known, would make him or her unsuitable as donors.

4. The committee considers that the management of donated gametes and embryos should be regulated by a national authority.

DONATION OF GENETIC MATERIAL FOR HUMAN REPRODUCTION

1. The donation of genetic material whether sperm, oocyte or pre-embryo, in order to create a child raises a number of ethical as well as social, religious, and legal issues.

2. Genetic material donation has been mainly used to treat infertility. It has also been used in the treatment of ovarian failure, the management of habitual abortion, genetic disorders, for ejaculating dysfunction, for single women wishing to have a biological child and for the achievement of postmenopausal fertility.

3. In practicing genetic material donation it is necessary to consider the interests of the child as well as those of the recipient couple and the donor. For this reason some countries forbid genetic material donation to single women. The committee considered this to be primarily a cultural/legal decision.

4. In countries permitting genetic material donation there is a need for regulation regarding the relation between the biological and social parents, the banking and disposal of genetic material (e.g. legal status of the pre-embryo), the safeguarding of the interests of the child, the quality of the medical management, and rules respecting record keeping.

5. The donation of genetic material should be altruistic and free from commercial exploitation.

Note : Donation of genetic material for human reproduction, IJCIO, 1993*

Reasonable compensation for legitimate expenses is appropriate. No genetic material should be used for donation without the formal written consent of the donor, the recipient and the recipient's legal partner (except in the case of single women). Withdrawal of consent must be accepted in certain circumstances (e.g. divorce).

6. Donors of genetic material should be healthy persons of normal reproductive age who are free from sexually transmitted diseases and hereditary disorders. Genetic material from a dead person should not be used unless a written statement by the donor exists. Members of the medical team involved in the management of a recipient should not be donors.

7. The number of donations from any single donor should be limited in order to avoid the future danger of consanguinity-and/or incest.

8. Donated genetic material should not in general be used to extend the natural reproductive lifespan because of the potential risk to the woman.

9. While donors of genetic material may occasionally be known to recipients (e.g. family members), usually they will be anonymous; in which case confidentiality must be preserved indefinitely unless permission to reveal identity is agreed and given by the donor, the recipient, and the recipient's legal partner.

ETHICAL ASPECTS OF THE MANAGEMENT OF SEVERELY MALFORMED NEWBORN INFANTS

1. The Committee recognized that newborn infants with severe malformations have the right to be allowed to die with dignity, without inappropriate or futile medical intervention when it is the considered view of both the parents and their doctors that this course is in the child's best interest.

2. The qualification "severe" is used in this context to indicate malformations that are either potentially lethal or whose nature is such that even with medical treatment they were likely, in the view of the parents and their medical advisors, to result in unacceptable mental and/or physical disability.

3. The Committee considered active euthanasia to be ethically unacceptable even when it appeared to be in the best interest of the child. However, the withholding or withdrawal of medical care (e.g. artificial ventilation, antibiotics, naso-gastric feeding, supplemental oxygen) was justified in such circumstances, provided that comfort care, including the offer of oral feeds, warmth, love and respect was maintained. The use of analgesics and sedative drugs to relieve distress and suffering was considered appropriate provided that their primary aim was not to cause death.

4. The individual decision to withhold or withdraw medical care should be made in the interest of the child and should not be determined by matters such as the sex of the infant or by eugenic, demographic or financial factors.

5. Prior to discussing the possibility of withholding or withdrawing medical care, the medical team has a responsibility to fully investigate and document the status of the malformed infant and to counsel the parents on their baby's condition, prognosis and on the management options.

6. However, when a malformed infant fails to breathe at birth, it is ethically acceptable to withhold resuscitative measures when the anomaly is of a severity that precludes doubt as to the wisdom of prolonging life. When doubt exists, resuscitation should be undertaken and medical care given until further investigation and consultation with the parents and colleagues has

been sought.

7. Usually the doctor counselling the withholding or withdrawal of medical care should be the most senior available. When appropriate the doctor may wish to consult with colleagues or with an ethics committee. The doctor should discuss the problem and intended actions with other members of the healthcare team, including the nursing staff.

8. In counselling parents the doctor should be careful not to impose his or her own cultural and religious prejudices on those whose beliefs and practices may be different, bearing in mind the legal requirements of the country. When a doctor's beliefs prevent the disclosing of all the possible options to the parents, the doctor has a duty to refer them to a colleague who is able to do so.

9. In discussing their problem, parents should be encouraged to seek advice from others. When appropriate they should be positively encouraged to seek further professional advice. They should always be given the opportunity of speaking together in private before reaching a decision.

10. The doctor counselling parents may not necessarily be seeking an outright decision but rather may be trying as sensitively as possible to gain insight into their wishes and hence to spare them avoidable distress and feelings of guilt.

11. When the two parents do not agree with each other as to whether or not to withhold or withdraw care, medical treatment should be pursued until the situation clarifies either because of changes in the baby's status or as a result of further counselling and discussion. Only as a last resort, in exceptional circumstances and after all other options have been exhausted, should the problem be referred to the courts.

12. When a decision has been taken to withhold or withdraw life sustaining care, all actions taken and the reasons for them, as well as the clinical course of the child, should be carefully documented.

13. After death following the withholding or withdrawal of medical care, the medical team has an ethical responsibility to request parental consent for a necropsy examination in order to confirm and complete the diagnosis, with a view to further counselling the parents and advising them on the outlook of future pregnancies.

ETHICAL ASPECTS OF HIV INFECTION AND REPRODUCTION

1. HIV infection is a transmissible disease with profound social and psychological implications for the woman, her partner and her family as well as for the health care team and society. Its characteristics include a prolonged latent period, a very high morbidity and mortality and social stigma. In addition, there is as yet no vaccine or curative treatment. Vertical transmission from mother to fetus, or to infant via breastmilk may occur. The incidence of this transmission may be reduced by drug therapy.

2. These facts bring sharply into focus the ethical conflict between patient privacy and confidentiality and the need to protect the sexual partners, the health care team and the public from a fatal communicable disease.

3. Because the disease has the potential of reaching epidemic proportions, the overriding consideration of infection control for the whole population comes into tension with the limits of individual rights. As well as aggressive educational programmes, other measures that may be considered would be mandatory offering of antenatal screening and confidential disclosure of HIV status to sexual partners and to health care workers at risk of exposure. Information

regarding numbers of seropositive individuals should be made available to public health officials.

4. Individuals who are informed of positive serostatus suffer severe psychological sequelae including the sense that they have been given a death sentence. Furthermore discrimination based on seropositivity in regard to housing, jobs and insurance exists. Physicians have a duty, therefore, to provide not only individual counsel and care for patients but also public advocacy to protect them from unfair and punitive actions.

5. While appreciating the importance of confidentiality and patient privacy, the ethical responsibility of individual patients to prevent harm to others still exists. Informed consent must be obtained prior to testing for HIV infection and communication of the resultant information. Every effort should be made through counseling to convince individual patients of their responsibility to others including the importance of allowing such information to be used to protect sexual partners and health care workers. If in spite of every effort, consent is not obtained and the risk of transmission is high in certain circumstances, with consultation, it may be justified to override patient confidentiality.

6. Assisted reproductive technology requires the elective donation of gametes, embryos or surrogate carriage of pregnancy. Because of the elective nature of this technology confidential counseling and testing can be done and inclusion of only those with negative HIV status is possible. To protect the interests of those at risk of unwanted exposure to HIV including the potential child, only seronegative individuals should be allowed to participate.

7. Breastfeeding : In societies where safe, affordable alternative methods of infant feeding are available, it may be unethical for an HIV infected mother to breastfeed her child. Where the risks of alternative infant feeding are high, the balance of risk to the infant may favour making breastfeeding ethically justified.

ETHICAL GUIDELINES REGARDING ALTERING GENES IN HUMANS

1. Rapidly advancing scientific information about the human genome and a growing ability to manipulate DNA have raised many issues as to how this genetic knowledge should be applied to people. Since the application of scientific knowledge to human reproduction lies within the sphere of obstetrics and gynaecology, it is important that practitioners in these fields be aware of the many important ethical implications raised by potential uses of genetic.

2. The term "gene therapy" has been used to refer to the alteration of human DNA for various purposes. This is misleading ; it is essential to recognize that not all alterations are "therapy". Only when the genetic alteration is made in order to alleviate suffering in an identified individual with a disease can it properly be termed "gene therapy".

3. Alteration of human genes can be thought of in three categories, each of which has different ethical implications. These are genetic alteration of somatic cells to treat disease (gene therapy), germ line genetic alteration and non therapeutic genetic alteration (genetic enhancement).

4. Genetic alteration of somatic cells to treat disease

(i) Since the altered genetic material is not inserted into the germ cells, the alteration is not passed on to future generations. Somatic genetic alteration raises many important issues, in the same way that research in humans on some other new experimental therapies does. For this reason, any research projects proposing to alter

the DNA of somatic cells of human subjects for therapeutic purposes should receive prior review and approval by a properly constituted research ethics board under a national authority (as described below). Aspects to be evaluated in the review should include detailed data on safety and risks, on whether there is fully informed consent, and on measures to protect confidentiality.

(ii) Such research projects alter-altering DNA in somatic cells should only be considered for serious disorders which cause major debilitation or early death, and that cannot be treated successfully by other means.

(iii) If the results of these gene therapy research projects are successful, future proposals may be made to use somatic cell gene alteration in the fetus in utero. Such proposals should have additional to ensure the autonomy of women is respected and that an adversarial relationship between a woman and her fetus is not created.

5. Germ line genetic alteration

This involves changing the gametes of an individual so the genetic change is passed on to subsequent generations. There are at present no techniques available to alter specific genes precisely, reliably and safely. When prospective parents have mutant genes it is possible to identify among their zygotes those which have not inherited the mutant allele(s). They have the opportunity to have their normal zygotes implanted in the uterus. Given the current and immediately foreseeable state of knowledge, it is safer and more appropriate to transfer to the uterus zygotes unaffected by the disease gene, than to identify affected zygotes, try to alter their DNA and implant them. Therefore, at the present, research involving alteration of the DNA of human zygotes, or of egg or sperm used to form a zygote which is to be implanted in the uterus is not ethically acceptable and therefore should not be permitted.

6. Non therapeutic genetic alteration (Genetic enhancement)

This involves the attempt to enhance or improve an already healthy genetic makeup by inserting a gene for improvement (for example, height, intelligence, eye colour). Many questions have been raised about criteria for this kind of technolgy, and what the social consequences would be of allowing the market place to determine how such technology would be used.

There is potential for profit ill marketing such technologies : yet this is a field where individuals do not have the knowledge to protect their own interests. The risks involved, with no sufficient justification for undergoing these risks, mean that research in human subjects involving the alteration of DNA for enhancement purposes is not ethically acceptable and therefore should not be permitted.

7. In summary, it is clear that the application of genetic alteration to human beings raises the likelihood of harm and exploitation of individuals. Because of this, all countries have a duty to put in place limits and to put in place a legally based authority to oversee and to ensure accountability for activities in this field.

ETHICAL ASPECTS OF THE INTRODUCTION OF CONTRACEPTIVE METHODS FOR WOMEN

1. The principle of beneficence requires that new contraceptive methods must be safe, effective, and acceptable to women.

2. In introducing new contraceptive methods, medical practitioners must be guided by respect for an individual's autonomy. This respect for autonomy is reflected in international standards of reproductive rights.

3. The same respect for autonomy requires

that standards especially relevant to the introduction of new methods of fertility regulation should include both facilitating informed choice, and delivering quality care.

4. Informed choice is a process by which a woman can freely make decisions about possible health intervention and which places decision-making in women's hands so that they can exercise their rights. The foundation of informed choice is information which is "accurate, unbiased, complete and comprehensible".

5. Respect for informed choice requires-that certain information on contraceptive methods should be provided to every woman considering using them, including :

- proper use
- contra-indications
- effectiveness in preventing pregnancy
- need to continue to protect against sexually transmitted infections
- possible side-effects
- possible interaction with other drugs or conditions

6. Respect for women's autonomy requires that each woman should be explicitly informed that at any time she can decide to stop using the method she chooses (e.g. she should be able to have an intra-uterine device or implantable contraceptives removed on request).

7. Healthcare practitioners are ethically required to work to eliminate obstacles to informed choice. To that end, among other efforts, power imbalances must be acknowledged and minimized. Staff must be well-trained, alternative methods of conveying information must be in place in order to respond to women who cannot read; staff biases and objections to methods of fertility regulation must not be conveyed to patients.

8. The duty to benefit patients requires that an important goal of practitioners should be to offer contraceptive methods within the context of high duality reproductive and sexual health services.

There are two major aspects to this : medical duality requirements, and the need to take into account women's expressed wishes. Firstly, medical quality requirements include that a range of appropriate contraceptive methods is offered, that appropriate supportive counselling services are available, and that providers are technically competent. The second aspect requires that interpersonal relations with healthcare personnel be respectful and take into account women's input and opinions.