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Clinical and Metabolic Study of a New Monophasic Formulation Containing Ethinylestradiol and Gestodene

Pramuan Virutamasen MD,
Damrong Reinprayoon MD,
Kamthorn Pruksananonda MD,
Rachanee Wongvathanavikrom,
Rosalin Kriengsinyos.

Human Reproduction Unit,
Department of Obstetrics and Gynaecology, Faculty of Medicine,
Chulalongkorn University,
Bangkok 10330, Thailand

Abstract : *Clinical and metabolic parameters were studied in healthy Thai women who took a new monophasic oral contraceptive formulation containing 30 mcg ethinylestradiol and 75 mcg gestoden (Δ -15-levonorgestrel) over 12 cycles.*

One hundred and seven patients were included in the clinical evaluation which covered a total of 913 woman-cycles. No accidental pregnancy occurred. Cycle control was excellent and body weight and blood pressure were not affected during one year of pill use. Continuation rate after 12 months was 70.9 per cent.

Of the 107 patients evaluated, 15 were included in the metabolic investigation which consisted of serial determinations of plasma glucose and insulin during periodic oral glucose tolerance testing (OGTT), serum cholesterol and lipoproteins and coagulation and fibrinolytic factors. Determinations were done at baseline, cycle 3, 6 and 12. There were small changes in plasma insulin and blood glucose levels during the OGTT. The minimal changes in lipid metabolism included a rise in triglyceride concentration and a decrease in LDL, HDL and total cholesterol. APTT, PT and Factor VII remained unchanged throughout the cycles but the AT III levels significantly decreased. (Thai J Obstet Gynaecol 1989 ; 1 : 81-9.)

Key words : clinical and metabolic study, monophasic formulation, ethinylestradiol, gestodene

Since combined estrogen-progestogen oral contraceptives (OCs) became available in the 1960s, an estimated 60 million women are currently using this method of contraception which to date, still represent the most effective reversible means of contraception.

The present formulations of combined OC pills differ from the earlier preparations in two respects: a lower dose of ethinylestradiol and the use of more appropriate progestogens. The

gonan class of progestogens has become the standard component through the years. Gestoden (Δ -15-levonorgestrel) is a new progestogen from the gonan class. Multicenter clinical and metabolic studies involving more than 19,000 woman-cycles of use with an OC formulation containing 75 mcg gestoden combined with 30 mcg ethinylestradiol showed high contraceptive efficacy, good cycle control and good patient acceptability[1-2].

This present study aims to evaluate the clinical and metabolic effects of this monophasic gestoden-ethinylestradiol combination in Thai women.

Patients and Methods

Healthy Thai women aged between 18 and 40 years old consulting at the Family Planning Clinic of the Department of Obstetrics and Gynaecology, Chulalongkorn University Hospital were considered eligible for inclusion in the study. Eligible patients were appraised of the objectives of the study and those consenting to take part in the study underwent complete history taking and physical examination including cytological evaluation. All patients without any of the exclusion criteria stipulated in the trial protocol were instructed to take the OC formulation which came as a standard calendar pack of 21 tablets containing 75 mcg gestoden and 30 mcg ethinylestradiol per tablet. A tablet was taken everyday starting on the first day of the menstrual cycle followed by a 7-day tablet-free interval. The patients took the pill for 12 cycles and were asked to come back for evaluation at cycle 3, 6, 9 and 12. Standard case report forms were used to record baseline parameters and subsequent findings through the treatment cycles. Clinical and gynaecologic parameters that were observed include incidence of accidental pregnancy, changes in blood pressure and body weight, cycle control (i.e., cycle length, amount and duration of bleeding, and incidence of breakthrough bleeding and spotting) and subjective and objective complaints.

Fifteen patients participating in the clinical evaluation were further evaluated as regards changes in laboratory parameters pertinent to carbohydrate and lipid metabolism as well as coagulation and fibrinolytic factors. The patients fasted at least 12 hours prior to venepuncture. Plasma insulin and glucose levels were measured before and after a glucose load of 75 g and then after 30 min, 1 hour, 1 1/2 hours, 2 hours and 3 hours. Plasma glucose was measured by the oxidase-peroxidase method. Plasma insulin was determined by radioimmunoassay.

Cholesterol and triglyceride determinations were carried out with the CHOD-PAP enzymatic test. Lipid fractions were separated by ultracentrifugation and apolipoprotein levels were determined using immunochemical assays. Blood coagulation and fibrinolytic factors were determined using standard commercial kits.

Data were analyzed using the statistical package for the social sciences (SPSS) utilizing paired *t* - test and other parametric tests, as appropriate, to test

statistical significance of the changes through the treatment cycles.

Results

Clinical parameters

One hundred and seven healthy Thai women were included in the clinical study. The patients went through 12 treatment cycles for a total of 913 woman-cycles of observation. The baseline paremeters are shown in Table 1.

Despite errors of tablet-taking in 2 per cent of cycles, no accidental pregnancies occurred.

Cycle length progressively shortened throughout the treatment cycles and duration of bleeding likewise reflected shorter duration of cycles, Table 2.

Plasma lipid and apolipoprotein fractions were evaluated as follows :

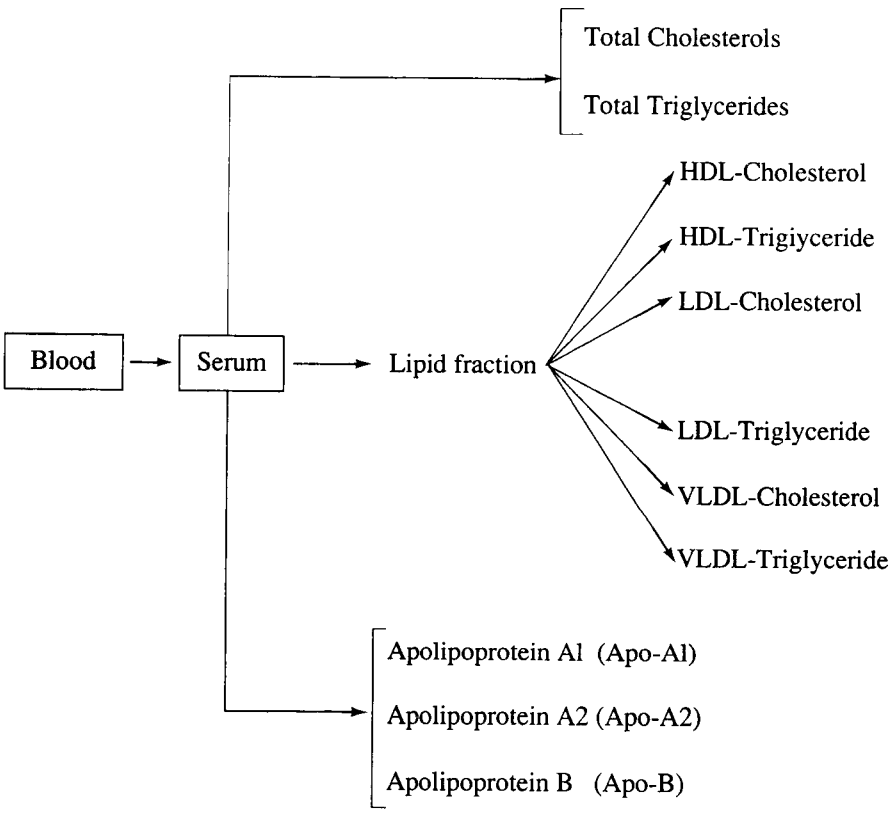

Table 1 Clinical data of the volunteers

Mean age (yrs)	25.2 (19-35)
Wight (kg)	50.5 (38-63)
Height (cm)	153 (142-164)
Quatelet index	22.9
Parity	0 - 2

Table 2 Changes in the clinical parameters throughout the cycles (mean values and % change from baseline)

	Mean cycle length (days)	Mean duration of bleeding (days)	Mean body weight(kg)
Pretreatment	30.5	4.2	50.5
Cycle 3	26.3	3.8	49.5
Cycle 6	28.4	3.9	49.7
Cycle 9	28.3	3.8	49.2
Cycle 12	28.3	3.8	50.2

Mean body weight showed minimal changes throughout the treatment cycles and these were all within < 1 kg weight fluctuations, Table 2.

Changes in blood pressure throughout the treatment cycles are reflected in Table 3. There were no clinically significant changes in both the systolic and diastolic pressures, with an overall mean percentage change from baseline equal only to 5 and 1 per cent respectively.

Table 3 Blood pressure changes (mean and % change from baseline)

	Systolic BP (mm Hg)	Diastolic BP (mm Hg)
Pretreatment	111.9	66.5
Cycle 3	106.3 *(-5.0%)*	68.1 *(+2.4%)*
Cycle 6	106.0 *(-5.0%)*	68.1 *(+2.4%)*
Cycle 9	104.2 *(-6.9%)*	64.8 *(-2.6%)*
Cycle 12	107.4 *(-4.1%)*	67.7 *(+1.8%)*
Overall mean change	*-5.25%*	*+1.0%*

Minimal side effects were noted during the study. Of the 50 patients who dropped out by the end of the study period, only 8 (16 per cent) were due to medical reasons or unwanted effects; 25 (50 per cent) were lost to follow-up and 17 (34 per cent) were due to personal reasons not related to the treatment or medication. Figure 1 shows the life table analysis throughout the treatment cycles. Continuation rate after 12 months was 70.9 per cent.

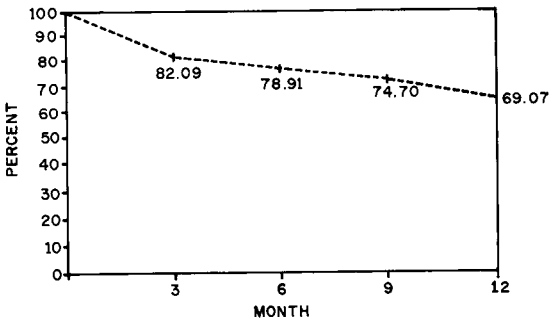

Fig. 1 Life table analysis

Metablic parameters

Fifteen volunteers underwent serial serum determinations of blood glucose and insulin during periodic oral glucose tolerance testing; cholesterol and lipoproteins; and coagulation and fibrinolytic factors.

Table 4 shows the results of the oral glucose tolerance tests done at baseline, cycle 3, cycle 6 and cycle 12.

Table 4 Blood glucose (mg/dl) and insulin levels (μu/ml) during the OGTT

	0 Min.	30 Min.	60 Min.	90 Min.	120 Min.	180 Min.
Baseline						
glucose	83.77	128.08	125.46	112.46	111.08	94.54
insulin	13.38	68.10	67.26	61.16	68.09	39.73
Cycle 3						
glucose	81.92	136.54	139.69	+ 132.00*	123.54	+ 103.46*
insulin	14.45	78.05	75.03	+ 85.14*	85.07	53.88
Cycle 6						
glucose	86.58	131.25	136.25	+ 133.67*	+ 130.08*	104.58
insulin	13.68	60.12	62.13	69.84	84.32	60.19
Cycle 12						
glucose	81.30	136.15	144.77	+ 138.54*	127.85	+ 101.54*
insulin	13.60	82.65	85.49	+ 86.57*	+ 105.05	64.36*

*statistically significant difference form baseline, $p < 0.05$

Compared with baseline there was statistically significant elevation of blood glucose levels at the 90th minute for cycle 3, 6, and 12. There were corresponding increases in plasma insulin which was significant for cycle 3 and cycle 12. Overall the area under the glucose concentration-time curve during the periodic OGTT (AUC) remained within the normal range.

Table 5 shows the cholesterol and lipoprotein determinations throughout the treatment cycles. Total cholesterol showed a consistent reduction throughout the cycles as well as HDL-C and LDL-C. Cholesterol VLDL showed a slight increase together with the triglycerides and its subfractions.

Table 5 Cholesterol and lipoprotein levels before treatment and at the end of the study

	Pretreatment levels (Mean)	Cycle 12 (Mean and % change from baseline)
Chol. VLDL*	.63	.65 (+ 3.2%)
Chol. LDL*	2.66	2.48 (-6.8%)
Chol. HDL*	1.53	1.43 (-6.5%)
Total chol.*	5.13	4.64 (-9.5%)
Trigly. VLDL*	.52	.60 (+15%)
Trigly. LDL*	.26	.35 (+ 34.6%)
Trigly. HDL*	.20	.28 (+ 40%)
Total trigly.*	1.14	1.51 (+ 32.5%)
HDL-C/Apo AI	.43	.37 (- 13.9%)
Apo B/Apo AI	.65	.52 (+ 20%)
Apo AI (mg/dl)	138.20	156.30 (+ 13.1%)
Apo AII (mg/dl)	26.80	34.20 (+ 27.6%)
Apo B (mg/dl)	86.50	78.90 (-8.8%)

*mmol/L

Table 6 Coagulation and fibrinolytic factors

	Pretreatment	Cycle			Overall
	(Mean)	3	6	12	Mean % change
		(Mean and % change)			
APTT (sec)	39.2	38.2 *(-2.5%)*	38.5 *(-1.7%)*	39 *(-0.5%)*	*(-1.6%)*
PT (sec)	11.9	11.8 *(-0.8%)*	11.6 *(-2.5%)*	11.7 *(-1.6%)*	*(-1.6%)*
TT (sec)	11.4	11.0 *(-3.5%)*	11.7 *(+6.1%)*	12.0 *(+5.3%)*	*(+2.6%)*
AT III (IU/ml)	49.1	29.6 *(-39.7%)*	32.4 *(-34.0%)*	20.9 *(-57.4%)*	*(-43.7%)*
Factor VII (%)	116.7	118.0 *(+1.1%)*	123.6 *(+5.9%)*	123.8 *(+6.1%)*	*(+4.4%)*

Table 6 shows the values of the coagulation and fibrinolytic factors. There were no significant changes in the values of APT/PT and Factor VII. Thrombin time was slightly increased at cycles 6, and this only reflects a mean increase of 2.6 per cent from baseline. Antithrombin III showed a significant decrease throughout treatment cycles.

Discussion

The long-term efficacy, acceptability and safety of any drug may only be established through epidemiological cohort studies. However, short of undertaking these extended, long-running investigations, a well-conducted clinical and metabolic assessment of changes occurring among a group of patients within a limited period of observation may suffice to evaluate new and promising drugs, especially when results from different centers turn out to be consistent and reproducible.

Gestoden, the newest progestogen from the levonorgestrel class, appears to possess favorable properties which allow halving of the progestogen content in a fixed combination pill when compared with the otherwise lowest-dose pills today[3]. Previous studies have demonstrated the OC formulation's minimal effects on the body's metabolic functions, combined with high contraceptive efficacy and acceptability. One British study has concluded that this gestoden-ethinylestradiol combination OC pill appears to be an ideal alternative to currently used OCs[1].

The results of the clinical parameters evaluated in this study are consistent with previous reports. Despite errors of tablet-taking in 2 per cent of the cycles, no pregnancy occurred and cycle control was excellent. Mean sys-

tolic pressure decreased throughout the cycles, with an overall mean percentage decrease of about 5 per cent after 6 cycles. This observation has been a consistent finding in similar gestoden studies and may not be what is expected, since earlier clinical experience with older, higher-dose OC formulations showed minimal but significant rise in BP among OC users and which reverted to normal after cessation of pill taking[4]. The mechanism apparently involves estrogenic stimulation of the renin-angiotensin-aldosterone mechanism (via increased hepatic synthesis of the renin substrate). Under physiologic conditions, the natural progesterone which possesses an aldosterone-antagonistic effect at the receptor level restores this imbalance caused by estrogens[5]. Gestoden is, as yet, the only progestogen shown to possess about 60 per cent of the aldosterone-antagonistic effect of the natural progesterone[6]. None of the synthetic progestogens used in OCs hitherto, possess this feature of gestoden. Previous clinical trials with gestoden-containing formulations have actually demonstrated normalization of previously elevated blood pressure in some women after taking this pill[7]. However, more evidence is needed to further confirm the clinical relevance of the unique pharmacological profile, especially in the low dose used in the pill.

Body weight remained unchanged; changes were within a kilogram which is well-within the normal physiologic weight variability of ± 2 kg.

The good tolerance and acceptability contributed to a very low drop-out rate of only 16 per cent after 12 cycles, due to medical reasons.

The mechanisms by which the hormones in OCs affect blood sugar levels are not exactly known. However, it has been demonstrated that plasma cortisol levels are increased in women taking OCs and this apparently causes the liver to release glucose into the blood stream, while at the same time inhibiting the utilization of glucose in the cells[8]. With OCs containing 50 mcg of estrogen and having high progestogen content, an overall risk of developing an abnormal OGTT was estimated to be 44 per cent among women with previous gestational diabetes[9, 10]. However, with a low-dose triphasic OC, Skouby and co-workers[11] found that none of their patients with previous gestational diabetes developed any worsening of the OGTT.

In this study, there was overall good tolerance to the glucose challenge as reflected in the area under the glucose concentration-time curve (AUC) remaining within normal limits. The small but statistically significant rises in plasma insulin are similar to the results obtained by Skouby and co-workers[11] among non-diabetics on low-dose OCs. The significance of this slight increase in plasma insulin during the OGTT is blunted by the unchanged areas under the curves. Interestingly, the values of plasma insulin before, during and after the OGTT, were all within acceptable limits throughout the cycle (normal value : up to 150 u/ml during OGTT).

The effect of contraceptive steroid on plasma cholesterol and lipoproteins

has been the topic of debates for years. Estrogens and estrogen-dominant pills increase serum hormone binding globulin (SHBG) and HDL-C, the latter presumed to be beneficial as regards the development of atherosclerotic disease. However, there are no data to show that lowering or raising HDL-C with OCs promotes or retards atherosclerosis or premature atherosclerotic disease[12]. Further, whatever appears to profoundly increase HDL-C, likewise may cause other metabolic effects, notably an imbalance in the coagulation and fibrinolytic factors[13, 14].

In this study, there were minimal although statistically significant changes in lipid metabolism, a rise in total triglycerides and a decrease in LDL, HDL and total cholesterol. These changes reflect that this OC formulation under study is not estrogen-dominant. An estrogen-dominant pill will show a profound increase in HDL-C and a more profound effect on coagulation and fibrinolytic factors. There were no significant changes in coagulation Factor VII. There was, however, a significant decrease in anti-thrombin III, a finding not consistent with previous studies. In the other reports, a net increase or only a slight nonsignificant decrease in the level of AT III was demonstrated[11, 16]. AT III works to antagonize the conversion of prothrombin to thrombin. If the AT III decrease was indeed significant, there should have been significant changes in the thrombin time (TT). In this study, there were no significant changes in the TT, as well as the thromboplastin time (PT) and the activated partial thromboplastin time (APTT). There is, therefore, reason to believe that this gestoden formulation has no adverse effects on coagulation and fibrinolytic system as previously reported[15-16].

Methodologically, however, a clinical investigation such as this present study has its limitations. As in similar studies, the drop-out rate was difficult to control. Although most of the drop-outs were not due to medical reasons, the number of evaluable and comparable patients progressively dwindled through the treatment cycles. Other limitations of the study include the limited number of patients, the limited observation time, and other extraneous variables like standardization of laboratory tests used, diet and psychosocial activities of the patients, and others.

Despite all these limitations, however, this gestoden-containing OC formulation proved its high contraceptive reliability, patient acceptability and minimal metabolic effects. Throughout the treatment cycles, the levels of the various laboratory parameters, despite the apparent fluctuations, all remained well-within the acceptable normal range.

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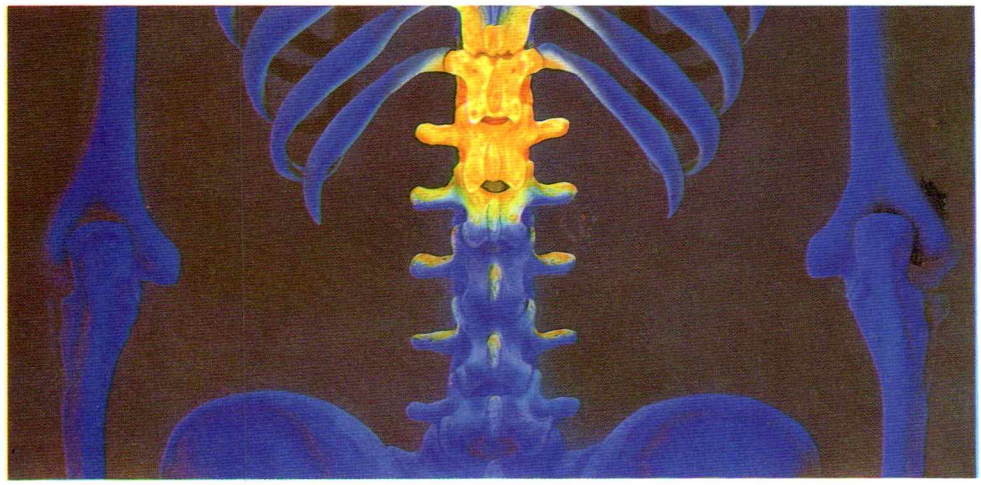

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Oral Medroxyprogesterone in the Treatment of Dysfunctional Uterine Bleeding : A Preliminary Report

Verapol Chandeying MD,
Sonthit Sutthijumroon MD,
Somchai Tungphaisal MD.

Department of Obstetrics and Gynaecology,
Faculty of Medicine,
Prince of Songkla University,
Songkla 90112, Thailand

Abstract : *The preliminary study of the effectiveness of oral medroxyprogesterone acetate was conducted among seventeen women with dysfunctional uterine bleeding at Songklanagarind Hospital from September 1988 to August 1989. The patients were treated with a dosage of 10 mg (one tablet) daily for ten days as initial hormonal hemostasis. After the first withdrawal bleeding, the menstrual blood flow was regulated for the next three cycles at a dosage of 10 mg daily from day 15 to day 24 of the cycle. The patients were evaluated by subjective description (menstrual calendar) for continuous observation (3 cycles after therapy).*

Twelve of the seventeen women (70.5 per cent) who had partial follow-up were satisfactory during treatment, and ten of the seventeen women (58.8 per cent) were satisfactory during treatment and post treatment. There were no adverse drug reactions. (Thai J Obstet Gynaecol 1989 ; 1 : 91-6.)

Key words : medroxyprogesterone acetate, dysfunctional uterine bleeding

Dysfunctional uterine bleeding (DUB) is abnormal bleeding that has no organic causes such as neoplasia, inflammation, or complication of pregnancy. Dysfunctional uterine bleeding results from a disturbance in hormonal secretory activity. Although the term has frequently been used to signify anovulatory forms of bleeding, it also describes disturbances in ovulatory forms of bleeding. While it has a nonorganic aetiology by definition, it can coexist with organic pathology, such as malignant and benign neoplasms[1].

Menorrhagia is usually a clinical diagnosis based entirely on the women's perception, and in many cases cannot be confirmed by objective measurement[2]. Oral medroxyprogesterone has been used for many years as one of the standard treatments for both ovulatory and anovulatory dysfunctional uterine bleeding[3-6]. In women with anovulatory cycles it seems reasonable to replace

progesterone in the cycle to make the periods regular and to offset the unopposed action of estradiol on the endometrium[7]. Because the bleeding results from an excess of unopposed estrogen, it is unnecessary to treat these patients with estrogen, either alone or in the form of oral contraceptives[8]. Medroxyprogesterone acetate (Provera) is an orally active synthetic progestin available in 5 and 10 mg tablets, that can be used instead of estrogen-progesterone combination cyclic therapy because of low adverse drug reactions. So, the aim of this study is to evaluate the efficacy of medroxyprogesterone acetate in the treatment of DUB.

Materials and Methods

Patients

The clinical trial included 27 patients with DUB treated with medroxyprogesterone acetate at Songklanagarind Hospital from September, 1988 to August, 1989. The patients' age varied from 18 to 39 years (mean 28.1 ± 5.8), parity was 0 to 3 (average 1), and 8 of 17 women were nulliparous. The common presentation was metrorrhagia and menorrhagia. Apart from history taking and routine pelvic examination, blood samples were drawn from all patients for serum prolactin determination. Endometrial biopsy with Novak's curette was performed on all but the nulliparous patients. The tissue was sent to the pathological department for an official report.

Treatment

The planned treatment was divided into 3 Phases. In Phase I, oral medroxyprogesterone acetate 10 mg daily was prescribed for initial hormonal hemostasis. After 10 days of treatment the drug was discontinued for progestational withdrawal bleeding to occur. The menstrual blood flow was regulated for the next three cycles (Phase II) by oral medroxyprogesterone acetate in a dosage of 10 mg daily from day 15 to day 24 of the cycle (the first day of bleeding was the first day of the cycle). And after that, in Phase III, bleeding was recorded on the menstrual calendar by the patients for the next 3 cycles to observe the regularity of the menstruation.

Hormonal assay

Serum prolactin measured by a radioimmunoassay method (Amersham, U.K.), depends on the competition for a limited number of binding sites on a prolactin-specific antibody between ^{125}I-labeled prolactin and prolactin in serum.

Patients' evaluation

The menstrual blood loss was evaluated by the menstrual calendar, which was designed for a subjective record of menstrual blood loss through the study by all women. In practice, the amount of bleeding expressed in terms of "light", "moderate", or "heavy" flow, so the record in each day of the calen-

dar was painted with red color, and corresponded with one, two, or three subsegments in each column respectively.

The criteria for satisfactory result was defined as after initial hemostasis and progestational withdrawal bleeding (phase II) the menstrual pattern returned to normal uterine bleeding, except the withdrawal bleeding which was occasionally delayed after discontinuing the medication.

Results

Among 27 patients, 10 were lost to follow-up. Data from 17 women were analysed by description, as shown in Table 1. The follow-up rate was 17 of the 27 women (62.9 per cent; 5 menorrhagia, 10 metrorrhagia, 1 metromenorrhagia and 1 oligomenorrhea) ; 12 women (number 1 to 12) had complete follow-up (Phase I + Phase II + Phase III), and 5 women (number 13-17) had partial follow-up (Phase I + Phase II). Of twelve women with complete follow-up, ten of them had satisfactory result, and of this satisfactory group, three of ten (number 1, 2, 7) had one cycle of oligomenorrhea due to delay of withdrawal bleeding.

Table 1 Subjective description in 17 women with a complaint of abnormal bleeding who were treated with oral medroxyprogesterone acetate

Subject number	Pretreatment complaint	**Phase I** Withdrawal bleeding before (-) or after (+) complete medication (days)	**Phase II** Cyclic regulation for 3 cycles 1st 2nd 3rd (Interval/duration)	**Phase III** Continous observation for 3 cycles
1	menorrhagia	+ 8	37*/4 25/7 29/7	satisfactory
2	menorrhagia	+ 7	37*/4 24/7 28/4	satisfactory
3	menorrhagia	+ 4	28/4 28/4 29/5	satisfactory
4	metrorrhagia	+ 4	27/4 28/4 27/4	satisfactory
5	metrorrhagia	+ 4	27/6 29/6 27/5	satisfactory
6	menorrhagia	+ 7	28/4 27/3 28/4	satisfactory
7	metrorrhagia	- 1	26/3 37*/4 29/4	satisfactory
8	metrorrhagia	+ 8	28/2 29/4 30/5	satisfactory
9	metrorrhagia	+ 1	23/5 32/1 31/6	satisfactory
10	oligomenorrhea	+ 2	27/5 28/4 27/4	satisfactory
11	metrorrhagia	+ 4	23/3 MTR MTR	unsatisfactory
12	metrorrhagia	+ 6	17*/4 MTR MTR	unsatisfactory
13	menorrhagia	+ 2	31/5 31/2 21/4	partial FU
14	metrorrhagia	+ 1	27/5 31/5 25/6	partial FU
15	metrorrhagia	+ 8	MTR MTR MTR	partial FU
16	metrorrhagia	MTR	MTR MTR MTR	partial FU
17	metromenorrhagia	MTN	MTN MTN MTN	partial FU

* = oligomenorrhea ; MTR = metrorrhagia, MTN = metromenorrhagia, FU= follow-up

Of five women with partial follow-up (only Phase I + Phase II), two of them (number 13, 14) had satisfactory result. Overall, 12 of the 17 women (70.5 per cent) were satisfactory during treatment, and 10 of the 17 women (58.8 per cent) were satisfactory (among these, case numbers 13, 14, 15, 16, 17, had partial follow-up) during treatment and posttreatment.

The efficacy of medroxyprogesterone acetate in the treatment of dysfunctional uterine bleeding was 88.2 per cent in Phase I (15 of the 17 women), 70.5 per cent in Phase II (12 of the 17 women), and 28.8 per cent (10 of the 17 women, in Phase III.

Three of the seventeen patients (17.7 per cent ; case numbers 2, 4, 11) had elevated serum PRL level (> 20.0 ng/ml), as shown in Table 2.

Table 2 Screen PRL level in dysfunctional uterine bleeding

Screen PRL level	Number	per cent
Elevated (> 20.0 ng/ml)	3	17.7
Normal	14	82.3

Table 3 shows the microscopic examination of the endometrium, and among these 4 of the 17 women (23.5 per cent) were virgin cases so that they had no sampling endometrial biopsy. There were proliferative endometrium in 8 of the 13 (61.5 per cent), secretory endometrium in 3 of the 13 (23.1 per cent), and atrophic endometrium in 2 of the 13 (15.4 per cent).

Table 3 Endometrial biopsy in dysfunctional uterine bleeding

Microscopic examination	Number	per cent
Proliferative	8	61.5
Secretory	3	23.1
Atrophic	2	15.4

There were no side effects of the drug among the patients treated with oral medroxyprogesterone acetate.

Discussion

The basis of hormonal hemostasis in the treatment of dysfunctional uterine bleeding is the administration of a large dose of synthetic progestin (progesterone). In a usual case of DUB, progesterone is lacking, and theoretically that is all that is required. The main problem of exogenous estrogen combined with progesterone in the treatment of DUB is that the medication may cause nausea and vomiting because of the estrogen content[9]. So the patient should be treated with progestin that will cause spiral artery constriction and result in normal progesterone-withdrawal menses. Since progesterone is not well absorbed orally, a progestin-like medroxyprogesterone in the form of Provera should be used. Studies of the morphology of the endometrium under the influence of progestins suggest that long term therapy (10-13 days) is needed to regress the proliferation[10]. Thus, medroxyprogesterone acetate 10 mg/day for 10-13 days per month is recommended.

In this study we used medroxyprogesterone at a dosage of 10 mg daily for ten days as the initial hormonal hemostasis and withdrawal bleeding, and

10 mg daily from day 15 to day 24 of the cycle as regulation for the next three cycles. The patient assessments by subjective description were satisfactory 10 of the 17 women (58.8 per cent) during treatment and posttreatment, and 12 of the 17 women (70.5 per cent) during treatment alone. Whereas the management should be medical in the first instance, if the problems recurred during therapy or during the subsequent follow-up period organic lesion shold be suspected. So the effectiveness of the treatment depends on the accurate investigation for pathologic DUB. Oral medroxyprogesterone is another drug as well as norethisterone which can be used in the treatment of DUB due to some advantages to exogenous estrogen. The so-called "post-pill amenorrhea syndrome" does not have any relation to estrogen therapy. Use of estrogen does not appear to increase the risk of myocardial infarction. On the contrary, its use increases HDL-cholesterol level and should be beneficial in this aspect.

It is now apparent that the only logical management of uterine bleeding caused by endocrine imbalance is hormonal. If a bleeding episode is caused by progesterone insufficiency, exogenous progestin will also be able to control it. The ideal hormonal agent to arrest and control an acute episode of dysfunctional bleeding, should have strong progestational, potent estrogenic, and mild androgenic properties. Of course, no single steroid compound has such activities. Pria et al[1] recommended a combination of ethinylestradiol 0.05 mg and norethindrone acetate 2.5 mg, given several times a day according to a decreasing dose schedule. Four tablets a day result in arrest of bleeding in most cases. The dose was then gradually decreased to 1 tablet a day for a total length of treatment of 10-16 days. The bleeding was arrested in over 75 per cent of patients within the first 48 hours. Withdrawal bleeding generally took place 1-4 days after termination of treatment, and the duration of flow was 4-5 days. A similar regimen employing other types of estrogen-progesterone preparations has been recommended[9]. Arrest of bleeding was usually observed within the first 48 hours in over 75 per cent of patients. In this study the arrest of bleeding was 88.2 per cent.

We had a preliminary evaluation to show that serum prolactin level may be valued in correlation with DUB. In normal adult women the range of serum prolactin concentration is 3-30 ng/ml[11], but our laboratory has set the the standard at less than 20.0 ng/ml. We found 3 of the 17 women (17.7 per cent) to have elevated serum PRL of more than 20.0 ng/ml, and that needs further study. Pepperell[12] found elevated prolactin levels in 7.6 per cent of women with oligomenorrhea. Hyperprolactinemia may also be associated with menstrual irregularities from defective corpus luteum function. So the prolactin and menstrual disorders are an interesting topic for further study.

Most of the patients (61.5 per cent) revealed proliferative endometrium compatible with some degree of estrogen stimulation. The progestin in the treatment of DUB is sufficient to change

the endometrium to secretory phase and followed by progesterone (progestin) withdrawal bleeding.

This study had some pitfalls; the amount of menstrual blood flow which was recorded by menstrual calendar is subjective data, and because the loss of patients follow-up was rather high. However, the results of the study did conclude that progestin was the alternative therapy to induce stabilizing predecidual stromal changes, followed by a withdrawal flow, the socalled "medical curettage". Some authors have suggested that in the treatment of dysfunctional metromenorrhagia or menorrhagia the duration of therapy may be increased to 10-14 days[3].

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Pulmonary Metastases in Gestational Trophoblastic Disease A Review of 223 Cases

Jialing Tang MD,*
Xingin Chen MD,*
Chuanchom Sakondhavat MD.**

* *Department of Gynaecologic Oncology, Guangxi Medical College Nanning, Guangxi, China*
***Department of Obstetrics and Gynaecology, Faculty of Medicine, Khon Kaen University, Thailand*

Abstract : *A study of epidemiological characteristics of patients with pulmonary metastases of gestational traphoblastic disease was carried out between 1970 and 1987 at Guangxi Medical College, Guangxi, China. Of 389 patients with malignant trophoblastic disease, 223 had pulmonary metastases. The ages of these patients varied from 20 to 58 and 88 per cent of them were multiparae. The antecedent pregnancies were molar pregnancy, full term pregnancy, abortion, and ectopic pregnancy which were encountered in 64.1, 21.0, 13.9 and 1 per cent respectively. The diagnosis of pulmonary metastases was made, in the mojority of cases, within one year after the termination of previous pregnancies. The mortality rate among these patients was 24.2 per cent. With the combination of surgery and chemotherapy, hysterectomy significantly reduced the mortality rate. The causes of death were cerebral haemorrhage, respiratory failure, abdominal bleeding, and unknown cause encountered in 59.3, 24.0, 7.4, and 9.3 per cent respectively. (Thai J Obstet Gynaecol 1989;1: 97-100.)*

Key words: pulmonary metastases, gestational trophoblastic disease

Trophoblastic disease is commonly encountered among Asian women. Pulmonary metastases is also frequently found but fortunately, it is easily accessible radiologically. It has been known for a long time that gestational trophoblastic disease has a poorer prognosis than that of non-metastatic ones[1].

Since the introduction of systemic chemotherapy for the treatment of gestational trophoblastic disease, the malignant disease has become the most commonly curable gynaecologic malignancy. Again, with the development of a sensitive assay for human chorionic gonadotropin (hCG), it has allowed this tumour to be monitored as well as being a marker during therapy and detecting the remission.

It is the purpose of this study to find out the epidemiological characteristics of patients with pulmonary metasta-

ses of gestational trophoblastic disease admitted to the Department of Gynaecological Oncology, Guangxi Medical College.

Materials and Methods

The analysis of medical records of women admitted to the Department of Gynaecological Oncology, Guangxi Medical College, for the treatment of pulmonary metastases of trophoblastic disease between 1970 and 1987 was carried out. The diagnosis of metastatic disease was made on the basis of the clinical and the radiological evidences in conjunction with the elevation of the urinary hCG levels. Particular attention was paid to the antecedent pregnancy, the interval between the diagnosis made and the previous pregnancy termination, the mortality, and clinical features of patients dying of pulmonary metastatic disease.

Results

There were 389 patients with malignant gestational trophoblastic disease admitted for treatment in this institute during the period of study. Among these patients 223 (57 per cent) had pulmonary metastases. The ages of the patients varied from 20 to 58 years and the majority of patients (65 per cent) were between 25 and 35 years. Multiparae were encountered in 88 per cent of patients while the highest parity was 16.

As shown in Table 1, 64.1 per cent of patients with pulmonary metastases of trophoblastic disease had a previous history of molar pregnancy. Again, these patients had malignant disease with pulmonary metastases within one year in the majority of cases after the termination of the antecedent pregnancies. With a longer period following the antecedent pregnancy the disease was encountered less fequently. One patient had the diagnosis made 21 years after her previous full term pregnancy. One hundred and twenty-six patients (56 per cent) presented with either chronic cough or hemoptysis while only 5 patients experienced pleuritic pain and haemothorax. The rest had the diagnosis made by chest X-ray examination. The overall mortality among these patients was 24.2 per cent.

Among 223 patients studied, only 113 had metastatic lesions confined only in the lungs while the rest had more than one metastatic sites: vagina (70), brain (36), liver (13), kidney (5), bladder (3), fallopian tube (3), vulva (2), intestine (2), and one of each of the following: ovary, arm, and diaphragm.

The treatments are shown in Table 2. Among patients who received no further treatment, no patient survived. Twenty-five patients defaulted and could not be traced, and are presumably dead.

Table 3 shows the clinical features of 54 patients dying of pulmonary metastases. Cerebral haemorrhage and respiratory failure were the major causes of death. Most of these deaths occured within one year.

Among the survivors, 12 subsequently had normal pregnancies follow-

Table 1 Antecedent pregnancy, interval of pregnancy termination and diagnosis of pulmonary metastases, and 2-year survival

Pregnancy	No.(%)	Pregnancy termination-diagnosis interval				Motality No.(%)
		<2	2-5	6-10	11+	
Molar prg.	143 (64.1)	108	33	2	-	27(18.9)
Term prg.	47 (21.0)	19	21	2	5	15(31.9)
Abortion	31 (13.9)	26	5	-	-	12(38.7)
Ectopic	2 (1.0)	2	-	-	-	-
Totals	223	155	59	4	5	54(24.2)

Table 2 Treatment

Treatment	No.(%)	Mortality(%)
Chemotherapy	85(38.1)	25 (29.4)
Chemotherapy and modified extensive hysterectomy	66(29.6)	6 (9.1)
Chemotherapy and total hysterectomy	59(26.5)	10 (16.9)
No treatment	13(5.6)	13 (100)
Totals	223(100)	54 (24.2)

Table 3 Clinical characteristics of 54 patients dying of pulmonary metastases of trophoblastic disease

Characteristics	No.(%)
Diagnosis-death interval(years):	
<1	42 (77.8)
1-2	12 (22.2)
Therapy:	
Chemotherapy only	25 (46.3)
Chemotherapy + surgery	16 (29.6)
No treatment	13 (24.1)
Metastatic sites:	
Lungs	4 (7.4)
Lungs and brain	32 (59.3)
Lungs and others	18 (33.3)
Causes of death:	
Cerebral haemorrhage	32 (59.3)
Respiratory failure	13 (24.0)
Abdominal bleeding	7 (7.4)
Unknown	5 (9.3)

ing chemotherapy. All children were apparently normal up until this report.

Disussion

Malignat trophoblastic disease may accompany or follow any type of pregnancy. The present study confirmed the previous knowledge that the most common preceding type of pregnancy of malignant trophoblastic disease is molar pregnancy. Again, it has been known for long that pulmonary metastases is commonly encountered among malignant trophoblastic patients[2, 3].

Since most of the patients with pulmonary metastatic trophoblastic disease had symptoms of chest pain, chronic cough, and dyspnea, the diagnosis was easily made radiologically. However, the diagnosis among those without symptoms was made by chest X-ray and elevated hCG levels. Thus, chest radiography plays an important role in the diagnosis of pulmonary metastases. With the availability of CT scan nowadays it allow us to disclose the presence of cerebral metastases as well as pulmonary ones.

Treatment of metastatic disease depends on multiple factors. However, combined chemotherapy is the universally accepted treatment[4]. Among 5 patients with haemothorax in this series, intrathoraxic metrotrexate was given with good results. However, it can be seen from this study, although not conclusive, that hysterectomy did significantly reduce the mortality rate despite reports that with extensive spread of the disease it is less responsive to therapy[5].

Since reports of death from toxicity of chemotherapy are negligible, the prognosis of this disease at present depends on the aggressive multimodel approach[6]. Death from cerebral haemorrhage is encountered frequently, thereby, chemotherapy should be given appropriately in order to prevent such a condition and hopefully prevent death.

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The Evaluation of Routine Pretreatment Investigation of Cervical Cancer Patients

Sayam Veskijkul MD,*
Vimol Sukthomya MD. **

* *Department of Obstetrics and Gynaecology*
** *Department of Radiology*
Faculty of Medicine, Prince of Songkla University,
Hat Yai, Songkla, 90112, Thailand

Abstract : *A retrospective study of 524 cases of cervical cancer at Songklanagarind Hospital from February 1982 to December 1987 was done. The purpose of the study was to evaluate the usefullness of the routine pretreatment investigation and to find out whether it makes any difference in final stages from the initial clinical stages or not. In clinical stage I, pretreatment investigation made no difference to the final stage. In clinical stage II, only 1 among 136 patients (0.7%) showed ureteric obstruction from IVP which caused the final stage to be changed to stage IIIb. In clinical stage III, chest x-ray showed metastases in 6 among 212 patients (2.8%) . IVP showed evidence of pelvic destruction in 2 among 211 patients (0.9%) . Cystoscopy showed bladder invasion in 7 among 175 patients (4%) and sigmoidoscopy showed an area of suspected tumor invasion in 2 patients : 1 proved to be pathologically negative for malignancy, while the other was not biopsied.*

From this study, we recommend only chest x-ray and IVP in all stages of cervical cancer patients while cystoscopy and sigmoidoscopy should be limited to patients at clinical stage III and IV or who have clinical indication. (Thai J obstet Gynaecol 1989; 1: 101-7.)

Key words : evaluation, pretreatment investigation, cervical cancer

Accurate pretreatment evaluation and staging of patients with cervical cancer is important as a determining factor for proper treatment and as a means of comparing therapeutic results. Traditionally, routine investigation consists of chest x-ray, intravenous pyelography (IVP), cystoscopy, sigmoidoscopy, complete blood count, renal and liver function tests and urine analysis[1-3]. If we do all, these are expensive, time consuming and important factors that can cause many patients to refuse treatment especially in underdeveloped and developing countries. Several studies have recommended that patients in an

early stage of cervical carcinoma should be routinely investigated by a chest x-ray and IVP, while cystoscopy should be reserved for advanced stages and sigmoidoscopy if clinically indicated such as hematuria, bloody stool, etc.[4-9]. However, this is still debatable. With today's emphasis on cost-effectiveness, it is necessary to justify the tests we order and to discard those making little contribution to the patient's care. This is a report of a retrospective evaluation of the usefulness of routine investigations for staging cervical cancer patients over a period of 5 years.

Materials and Methods

A descriptive study with retrospective design was performed in patients with invasive carcinoma of the cervix. The records of 613 patients were retrieved. Seventy-seven were excluded because they refused both pretreatment evaluation and treatment. A further twelve were excluded because of unknown staging due to previous initial treatment elsewhere. Thus 524 were eligible for evaluation. Each patient was evaluated by gynaecologists in the Gynaecologic Oncology service between 1982 and 1987 to give an "initial stage" based solely upon physical examination and cervical biopsy. General anaesthesia was not used during the process of clinical staging. Most of the patients received routine pretreatment evaluation including chest x-ray, IVP, cystoscopy, sigmoidoscopy, complete blood count, renal function tests and urinalysis either at the referal hospitals or at Songklanagarind Hospital. Some patients received only some parts of pretreatment evaluations and then refused because of the long time waiting for the appointment for some of the investigations. Staging was done according to the International Federation of Gynecology and Obstetrics (FIGO) classification system.

Results

Pretreatment evaluations are shown in Table 1. The number of patients in each initial stage is shown in Table 2 and pathological descriptions of the invasive cervical cancer in 524 patients are shown in Table 3. Most of the patients had squamous cell carcinoma and adeno-carcinoma with an incidence of 82.5 and 13.1 per cent respectively.

Table 1 Pretreatment evaluation in 524 patients of cervical cancer

Investigations	Number of the patients investigated	Per cent
Chest x-ray	428	81.7
IVP	408	77.9
Cystoscopy	316	60.3
Sigmoidoscopy	335	63.9

Table 2 Initial clinical staging of 524 cervical cancer patients

Stage	Number of patients	Per cent
Ia	15	2.8
Ib	68	13.0
IIa	12	2.3
IIb	157	30.0
IIIa	0	0.00
IIIb	258	49.2
IV	14	2.7
Total	524	100.00

Table 3 Pathological descriptions of invasive cervical cancer

Histology	Number of cases	Per cent
Squamous cell carcinoma	444	84.7
Adenocarcinoma	70	13.4
Adenosquamous	8	1.5
Undifferentiated carcinoma	1	0.2
Verrucous carcinoma	1	0.2
Total	524	100.00

Table 4 Results of chest x-ray in 428 cervical cancer patients

Clinical staging	Numberof cases	Normal chest x-ray	Pulmonary metastases	Non-tumor abnormalities
Ia	8	8	-	-
Ib	52	50	-	2
IIa	10	5	-	5
IIb	133	115	-	18
IIIb	212	169	6 (2.8%)	37
IV	13	8	2 (15.3%)	3
Total	428	355	8	65
Per cent	100	82.9	1.9	15.2

Chest x-ray was performed in 428 patients studied. The results are summarized in Table 4. Pulmonary metastases were found in 8 patients, all in advanced stages, 6 among the 212 were at the initial stage IIIb and 2 among the 13 were at the initial stage IV. Hence, the x-ray appearance altered the staging from IIIb to IV in 6/212 (2.8 per cent) patients, or to put it another way, we had to do a chest x-ray in 212 patients in an initial stage IIIb in order to alter 2.8 per cent of this staging. The character of pulmonary metastases includes infiltration, one or more nodules in the lung fields and pleural effusion. Non-tumor abnormalities were found in 65 patients (15.2 per cent). Cardiovascular abnormalities such as cardiomegaly and calcified tortuous aorta occured in 36 patients, while respiratory abnormalities such as tuberculosis, pulmonary infiltration, and atelectasis occured in 20 patients. Active tuberculosis was found in 7 patients (1.6 per cent). The rest of the abnormalities were scoliosis, old healed fractured rib and fractured clavicle.

Intravenous pyelography was performed in 408 patients studied. The results are summarized in Table 5. Unilateral ureteric obstruction was seen in 10.3 per cent and bilateral in 7.1 per

Table 5 The results of IVP in 408 cervical cancer patients

Stage	No.	Normal IVP	Urteric obstruction Unilat.	Bilat.	Total obstruction (by cancer)	Suspected bladder involved	Pelvic bone destruction
Ia	2	2	-	-	-	-	-
Ib	49	45	1*	-	-	-	-
IIa	10	8	-	-	-	-	-
IIb	126	107	3**	-	1(0.7)	1*	-
IIIb	211	122	37	23	60	6	2(0.9%)
IV	10	2	1	6	7	2	-
Total	408	241	42	29	68	9	2
Per cent	100	59.1	10.3	7.1	16.7	2.	0.5

* previous urologic surgery

** 2 cases of ureteric obstruction caused by ureteric calculi

\# cystoscopy showed no evidence of tumor invaded bladder mucosa

cent. One patient in stage Ib had unilateral ureteric obstruction which was thought to be due to previous urologic surgery. Three patients in stage IIb had unilateral ureteric obstruction but two of them proved to be due to ureteric calculi. Thus, only one unilateral ureteric obstruction in initial stage IIb patient was thought to be due to cervical cancer. Hence, the results of the IVP altered the staging from II to IIIb in 1/136 patients (0.7 per cent), 2 among 211 patients at the initial stage IIIb were shown to have bony pelvic destruction by the scout film of IVP. Hence, the IVP (scout film) altered the staging from IIIb to IV in 2/211 patients (0.9 per cent).

Cystoscopy was performed in 316 patients studied. The results are summarized in Table 6. No patients in stage I and II were shown to have suspected tumor invasion or even bullous edema while there was grossly suspected tumor invasion in stages IIIb and IV with an incidence of 7.4 and 14.3 per cent respectively. Nine among 13 patients who had grossly suspected tumor invasion in initial stage IIIb received cystoscopic biopsy and revealed pathologic tumor invasion in 7 patients. Hence, the cystoscopy altered the staging from IIIb to IVa in 7/175 patients (4 per cent).

Sigmoidoscopy was performed in 335 patients studied. The results are summarized in Table 7. There were 5 patients who had been suspected of tumor invasion, one patient was at the initial stage IIb but sigmoidoscopic bi-

Table 6 Results of cystoscopy in 316 cervical cancer patients

Stage	Normal/Exam	V-V* fist	Bullous edema	Suspected tumor involvement	Cystoscopic +ve	Biopsy -ve	Not biopsy
Ia	1/1	-	-	-	-	-	-
Ib	29/29	-	-	-	-	-	-
IIa	4/4	-	-	-	-	-	-
IIb	97/100	-	-	-	-	-	-
IIIb	141/175	-	14	13 (7.4%)	7 (4%)	2	-
IV	1/7	2	2	1 (14.3%)	1	-	-
Total	273/316	12	16	14	8	2	4
Per cent	86.4	0.6	5.1	4.4	2.5		

* V-V fist = Vesico-vaginal fistula

Table 7 Results of sigmoidoscopy in cervical cancer patients

Stage	Exam	Normal	Suspected tumor involement	Sigmoidoscopic biopsy +ve	-ve	Not biopsy
Ia	1	1				
Ib	32	32				
IIa	5	5				
IIb	104	101	1	-	1	-
IIIb	185	175	2	-	1	1
IV	8	5	2	2(25%)	-	-
Total	335	319	5	2	2	1
Per cent	100	95.2	1.5	0.6	0.6	0.3

opsy showed negative for malignancy in this case. Two patients were at the initial stage IIIb. Unfortunately, only one of these patients received biopsy and was shown to be negative for malignancy. The fourth and fifth patients were at stage IV due to rectovaginal fistula and were positive for malignancy from biopsy. Thus, the sigmoidoscopy in this study does not alter the staging.

Discussion

Most of the Thai patients who had carcinoma of the uterine cervix were in advanced stages. This was probably due to inadequate service of the government health care, the great number of uneducated patients especially in the old age group, the stigma placed on pelvic examination and because the symptoms in early stage cervical cancer were not severe enough to encourage appropriate attention on the part of the patients. Even in the advanced stages, up to 12.8 per cent of the patients refused to have pretreatment evaluation following a treatment programme. This was probably due to the time and money spent on complete evaluation, and the fact that patients usually come from provinces far away from a gynaecological center. They have to spend many days in or near the hospital before the evaluation is completed. Furthermore, they have most likely heard about the unsatisfactory results of treatment provided at the advanced stage. Thus, only 48.9 per cent (300/613) of the patients received complete pretreatment evaluation in this study. However, 524 patients (85.5 per cent) received treatment. Some of them received only some parts of the pretreatment evaluation. So, the purpose of this study is to evaluate the usefulness of the routine pretreatment evaluation in order to identify which tests may be omitted without compromising the patient's care.

The study of 428 chest films found that pulmonary metastases occured only in initial stage III and IV patients. However, we still recommend performing chest x-ray in all cases because pulmonary matastases can occur in early stages due to the high density of lymphatic and blood vessels in the parametrium. Other studies showed that pulmonary metastases occurred at stage II in about 0-1.9 per cent[4, 6, 8, 9]. The findings on pulmonary metastases influence the appropriate management, which usually requires systemic chemotherapy plus radiation. The result of treatment is much improved due to the advance in chemotherapeutic agents when compared to radiation alone[10]. Furthermore, chest x-ray can be performed easily, has no adverse effect, is not expensive, and is valuable for check up in Thai people because of the high incidence of asymptomatic pulmonary diseases such as tuberculosis in 1.6 per cent and pulmonary infiltration in 2.1 per cent in this study. These cause the chest film to be suitably performed in all cases of cervical cancer. The incidence of pulmonary metastases in this study is 1.9 per cent while from the other studies it ranged from 0.3-2.2 per cent[4, 6, 8, 9]. The character of radiographic abnormalities include infiltration, one or more nodules in the lung fields and pleural effusion. Sometimes the radiographic abnormalities

from pretreatment evaluation may be misread. Parker et al[11] showed that the follow-up chest films may eventually reveal tumor related abnormalities in approximately 6 per cent of patients with cervical cancer.

The study of IVP showed that the incidence of ureteric obstruction was related to the extent of the tumor detected by pelvic examination. Almost all of the patients who had ureteric obstruction were in clinically advanced stages except 1 among 126 patients (0.8 per cent) in the initial stage IIb. While the findings of ureteric obstruction from IVP does not influence accurate staging in patients who had initial stage IIIb, the scout film does, because it may show evidence of pelvic bone destruction which can alter stage IIIb to IV as shown in this study, i.e. 2 among 211 stage IIIb patients which represents 0.9 per cent. Thus, if we consider only accurate staging the IVP has probably little value other than the scout film in test. However, other studies have found that the incidence of ureteric obstruction in the initial stage IIb patients was approximately 0-7.5 per cent[4-6, 8, 9]. This may reflect the difficulty in the assessment of the parametrial extension by tumor from pelvic examination without anaesthesia especially in an obese patient and may be the reason why the incidence of ureteric obstruction in the initial stage IIb differs in this study from other study[12]. The knowledge of ureteric obstruction may require pretreatment urinary drainage such as percutaneous nephrostomy before radiotherapy. Also Photopulos et al[13] showed that routine posttreatment IVP is useful in early detection of recurrences of cervical cancer. Therefore, a baseline IVP should be performed because of the usefulness in the treatment plan and in the follow-up period.

From our study in cystoscopy no patients in stage I and II showed suspectd tumor invasion or even bullous edema. This confirmed the studies from other series which found tumor invaded bladder only in stage III and IV[4, 5, 7-9,]. The incidence of tumor invading the bladder in initial stage IIIb and IV ranged from 0-21.6 per cent and 0-90 per cent respectively. These incidences depend upon the number of patients in each stage and series. From our study, the incidence of gross tumor invading the bladder in stage IIIb and IV was 7.4 per cent and 14.3 per cent respectively. This means that about 7.4 per cent were upstaged by cystoscopy. However, this incidence was not exactly correct because there was pathologic confirmation of stage IIIb patients in about 70 per cent (7/13) of cases. If we rely only on the cases that are confirmed by pathology, the patients of the initial stage IIIb will be upstaged in only 7 among 175 patients (4 per cent). The study of Romero et al[7] showed that the incidence of tumor invading the bladder was reliable on when there was pathologic confirmation, because only 12 per cent and 24 per cent of the patients in stage IIIb and IV who had grossly suspected tumor invasion proved to be positive for malignancy by cystoscopic biopsy. In cases of frankly invasive cancer which were negative for malignancy from pathology,

the cystoscopic biopsy should be repeated but this will cause higher cost, morbidity and delay in treatment.

Based on our findings and from other reports[4, 5, 7-9], patients with clinical stage I and II of carcinoma of the cervix are lucky to have no significant bladder findings. Thus, we do not recommend the routine use of cystoscopy for staging of cases with stage I or II cervical cancer.

The incidence of abnormalities detected by sigmoidoscopy in patients with invasive carcinoma of the cervix is directly related to the extent of the tumor detected in the physical examination. This is the same as the results in the cystoscopy. Very few tumor related abnormalities were demonstrated by the sigmoidoscopy in this study. There were only two patients who had pathological confirmation of tumor invading the rectal mucosa and all of them were already in stage IV by initial staging. So, the final stage was not different from the initial stage after the sigmoidoscopy was performed. Other studies also showed that mucosal invasion is found only rarely in the advanced stage[4, 8, 9]. Thus, we no longer recommend it as part of our routine pretreatment but, instead, reserve it for those patients with specific indications such as chronic diarrhea, ulcerative colitis, etc..

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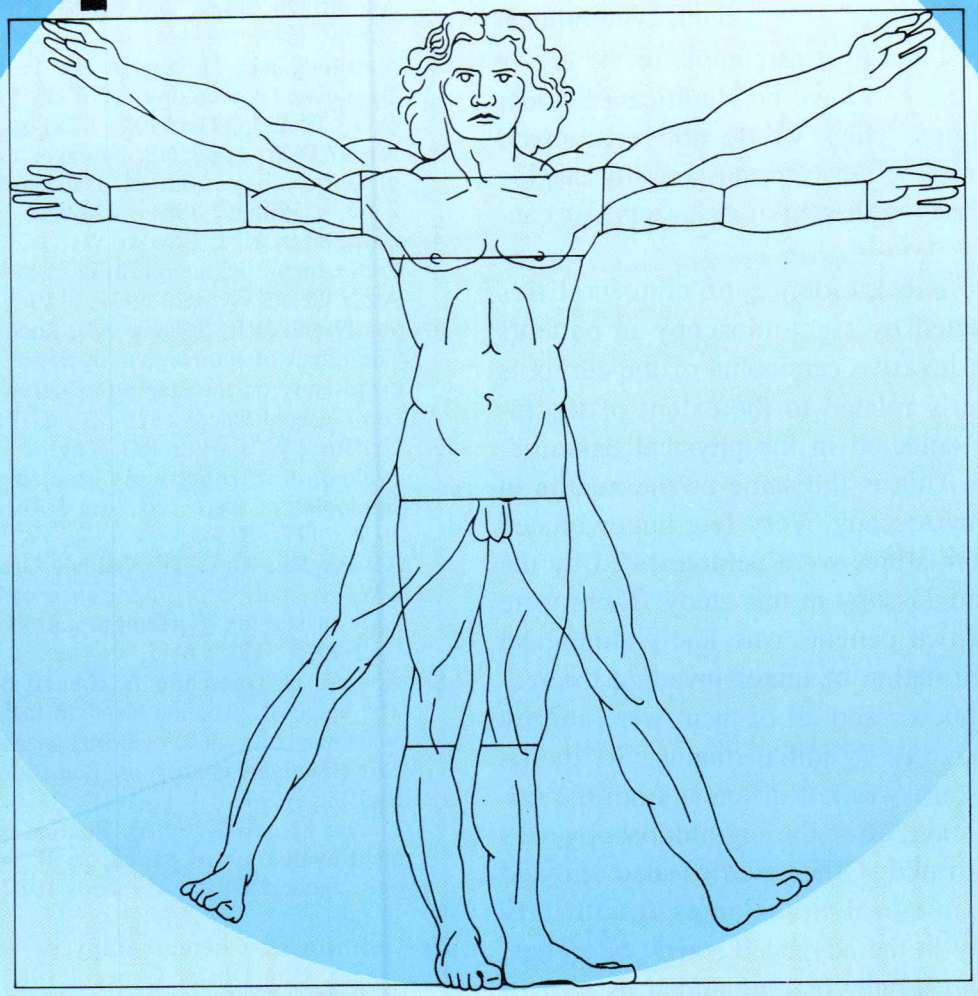

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KAP on Sexual Behavior, Contraception, and STD Prevention Among Some Hat Yai Teenagers

Somchai Tungphaisal MD,
Verapol Chandeying MD,
Sonthit Sutthijumroon MD,
Oermporn Krisanapan MS.

Department of Obstetrics and Gynaecology,
Faculty of Medicine, Prince of Songkla University,
Songkla 90112, Thailand

Abstract : *In the context of a high and increasing incidence of adolescent problems, a sample survey of Hat Yai teenagers on sexual awareness, knowledge, attitude and practice, including contraception and sexually transmitted disease, was conducted in June, 1989. Five hundred completed questionnaires, (from 250 males and 250 females), were sent back. The mean age of the students was 14.9 years. 22.8 per cent of the male students had sexual experiences with prostitute and/or girl-friends. Half of the students did not use any method for sexually transmitted disease (STD) prevention, while 42.1 per cent used condoms. The students had only a limited level of knowledge on STD and contraception. The most common sources of information were books and magazines. Most of the students, especially females, disagreed with the concept of premarital sexual intercourse because of culture and complications that may follow. About 15 per cent agreed with such a relationship for experience and learning how to prepare oneself for marital life. The most common problems related to reproductive health were masturbation and STD in males, and menstrual problems in females. A significant number of students (78.4 per cent) needed responsible persons to set up a framework, which was rather private and separated from routine hospital services, for information and counseling. Most of them agreed with the concept of a peer counselor. (Thai J Obstet Gynaecol 1989 ; 1 : 109-14.)*

Key words : KAP on sexual behavior, contraception, STD

At present, adolescents are one of the most important groups of the population in Thailand. Various problems, particularly about reproductive health, tended to be more violent. The reasons may be due to social changes towards western culture and the effect of the mass media which provokes sexual desire and sexual response rather than promoting education.

Several problems, such as unplanned pregnancy, illegal abortion, and sexually transmitted diseases (STD), have arisen because the adolescents did not

understand or misunderstood the reproductive and sexual development[1-4]. Though many studies about knowledge, attitude, and practice (KAP) on sex and reproduction of the adolescents have shown various similar problems[4-10], the subject of sex education has not yet been fully accepted to be taught in schools, especially in Thailand.

The purpose of this investigation was to find out the knowledge, attitude, and practice of some Hat Yai teenagers on sexual behavior, contraception, and STD prevention, as well as reproductive health problems and the need for reproductive health education and an adolescent counseling clinic.

Materials and Methods

The study population consisted of grade 7-12 students in a secondary school in Hat Yai. A questionnaire including general characteristics of the students, KAP on sexual behavior, contraception, and STD prevention, reproductive health problems, and the need for reproductive health education and adolescent counseling clinic.

One thousand questionnaires were distributed to students of the selected classes by school counseling teachers in June, 1989, after one of the survey team members had explained the purposes, general content, and confidentiality of the investigation. Only 500 of the 625 questionnaires returned were completed.

Results

General characteristics of the students

There were 500 students (250 males and 250 females) who completed the questionnaires. The overall average age was 14.9 years, being 14.8 years for males (range 13-18) and 15.0 years for females (range 13-18). Most of them (98 per cent) were Buddhists and had enough financial support.

Sexual experience and partners

Of the 500 students, there were 57 males (11.4 per cent of all or 22.8 per cent of male students) who had coitus, none of the females had. The sexual partners of the male students were prostitutes, girl-friends or both (Table 1).

Table 1 History of sexual intercourse by age and partner

Partners	Age (years)						Total (%)
	13	14	15	16	17	18	
Prostitutes	1	3	7	5	2	0	18 (31.6)
Girl-friends	2	10	7	4	3	3	29 (50.9)
Both	0	1	3	2	2	2	10 (17.5)
Total	3	14	17	11	7	5	57 (100.0)

Knowledge and prevention of STD

It was found that male students knew more about STD than did the females ($p < 0.001$), (Table 2). The major sources of information came from books, magazines, TV and radio. Other sources were friends, teachers, and parents (Table 3). 42.1 per cent of the students used condoms when having sexual intercourse with a prostitute, while 50.9 per cent did not protect themselves by any method (Table 4)..

Table 2 Distribution by sex of the students' knowledge about STD

Level of knowledge	Sex		Total (%)
	Male (%)	Female (%)	
Some	120 (48.0)	66 (26.4)	186 (37.2)
Only name	84 (33.6)	127 (50.8)	211 (42.2)
Don't know	46 (18.4)	57 (22.8)	103 (20.6)
Total	250 (100.0)	250 (100.0)	500 (100.0)

Table 3 Sources of information about STD

Sources	Sex		Total (%)
	Male(N=204)	Female(N=193)	
Books, magazines	69.6	76.7	72.0
TV, radio	67.6	73.1	71.3
Friends	29.4	10.9	20.4
Teachers	4.4	6.7	5.5
Others	3.4	9.3	6.3

Table 4 Distribution of methods of STD prevention by age

Methods	Age (year)						Total (%)
	13	14	15	16	17	18	
None	2	7	10	6	2	2	29 (50.9)
Condom	1	5	6	5	5	2	24 (42.1)
Others*	0	2	1	0	0	1	4 (7.0)
Total	3	14	17	11	7	5	57 (100.0)

*- washing penis immediately after intercourse
- urination immediately after intercourse
- taking antibiotic before or after intercourse

Knowledge about contraception

It was found that the female students knew more about contraception than did the males ($p < 0.001$), (Table 5). The main sources of information were books and magazines (Table 6).

Table 5 Distribution of the students' knowledge about contraception

Level of Knowledge	Sex		Total (%)
	Male (%)	Female (%)	
Some	72 (28.8)	112 (44.8)	184 (36.8)
Only name	131 (52.4)	92 (36.8)	223 (44.6)
Don't know	47 (18.8)	46 (18.4)	93 (18.6)
Total	250 (100.0)	250 (100.0)	500 (100.0)

Table 6 Sources of information about contraception (in percentage)

Source	Sex		Total (%)
	Male(N=203)	Female(N=204)	
Books, magazines	60.5	75.9	70.3
TV, radio	34.5	41.4	37.8
Friends	21.2	9.8	15.5
Teachers	5.4	8.4	6.9
Others	3.4	9.3	6.3

Attitude toward premarital sexual intercourse

Most of the students (69.6 per cent), particularly the females (90.4 per cent) disagreed with premarital sexual intercouse (Table 7). Reasons for disagreement ranged from the belief that premarital sex was against Thai culture to the fact that it might create many problems, such as STD, unwanted pregnancy, and illegal abortion.

For the students that agreed with such a relation, the reasons included the search for experience to prepare oneself for marital life, learning about each other, and to select a suitable partner.

15.6 per cent of the students had a neutral attitude. The reasons included individual rights and satisfactions, unex-

pected situations and the environment. It should be avoided if one was not ready for family life, but if it cannot, complications must be prevented.

Table 7 Attitude toward premarital sexual intercurse

Attitude	Sex		Total (%)
	Male (%)	Female (%)	
Agree	73 (29.2)	1 (0.4)	74 (14.8)
Disagree	122 (48.8)	226 (90.4)	348 (69.6)
Neutral	55 (22.0)	23 (9.2)	78 (15.6)
Total	250 (100.0)	250 (100.0)	500 (100.0)

Problems related to reproductive health

Problems or concern about reproductive health of the students are shown Table 8 and 9. Masturbation and STD were the main problems among male students while menstrual problems were the main concerns among females.

Table 8 Problems related to reproductive health among male students

Problems	Number (%)
No	173 (69.2)
Yes	77 (30.8)
Masturbation	59
STD	22
Unplanned pregnancy (in partner)	2
Others*	3
More than one problem	16
Total	250 (100.0)

* premature ejaculation, small penis, too much sexual desire

Table 9 Problems related to reproductive health among female students

Problems	Number (%)
No	190 (76.0)
Yes	60 (24.0)
Abnormal bleeding	47
Dysmenorrhea	25
Leukorrhea	6
Masturbation	4
More than one problem	12
Total	250 (100.0)

Need for adolescent counseling clinic

About 80 per cent of the students agreed with the concept of an adolescent counseling clinic to prevent or reduce sex-related problems. In addition to these general opinions, they felt that proper sex education should be given to students. The minority, who objected to the concept thought that it was not worthwhile because the students would not dare go to the counseling clinic and many other sources of information are available (Table 10).

Table 10 Need for adolescent counseling clinic

Need	Sex		Total (%)
	Male (%)	Female (%)	
Yes	208 (83.2)	184 (73.6)	392 (78.4)
No	42 (16.8)	66 (26.4)	108 (21.6)
Total	250 (100.0)	250 (100.0)	500 (100.0)

Attitude toward peer counselor

There were 75.2 per cent of the students who agreed with the concept of

a peer counselor, who had been trained for sex education and reproductive health, to discuss and solve the primary problems, because peers can understand students better. The minority that disagreed thought that the students are too young and do not have enough experience to manage the problems (Table 11).

Table 11 Attitude toward peer counselor

Attitude	Sex		Total (%)
	Male (%)	Female (%)	
Agree	198 (79.2)	178 (71.2)	376 (75.2)
Disagree	52 (20.8)	72 (28.8)	124 (24.8)
Total	250 (100.0)	250 (100.0)	500 (100.0)

Discussion

The present study demostrated that about one-fourth of the male students had sexual experiences while none of the females had. Half of these male students did not use any method of contraception and STD prevention, while 42.1 per cent used condoms. This may be due to the limited level of knowledge about contraception and STD prevention. The findings highlight the need for a variety of approaches to improve the knowledge and practice for further reduction of unprotected sexual intercourse.

Most of the students (69.9 per cent), particulary the females (90.4 per cent), disagreed with premarital sexual intercourse because of the culture and complications that may follow. Anyhow, about thirty per cent of all students agreed with or had neutral attitude toward premarital sexual intercourse with the reasons for experience to prepare oneself for marital life, learning about each other, and to select a suitable partner.

The growing trend toward increasing premarital sexual relationships indicates that a framework must be developed offering reproductive health information and counseling for adolescents. Of such a service, a climate must be created in which they feel free and confident enough to seek answers for their questions concerning sex and contraception or any other problems. A significant number of the students (78.4 per cent) also need responsible persons to set up an adolescent counseling clinic for this purpose.

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Clinical Course and Outcome of Pregnancies in Women with Hyperprolactinemia : Ramathibodi's Experience

Aram Rojanasakul MD,
Rudi Sirimongkolkasem MD.

Department of Obstetrics and Gynaecology,
Faculty of Medicine, Ramathibodi Hospital,
Bangkok 10400, Thailand

Abstract : *The clinical course and outcome of pregnancies in women with hyperprolactinemia were determined. There were 18 pregnancies in 15 patients who had been treated with bromocriptine and lisuride. Outcome of pregnancies were 12 full term, 2 induced abortion, 1 spontaneous abortion, 1 ectopic pregnancy, 1 dead fetus in utero and 1 preterm delivery. Tumor complications occured in 3 pregnancies of two patients. One patient with microprolactinoma had severe headache which was rapidly relieved by bromocriptine. The other patient developed severe headache in her first pregnancy and visual field defect in the second pregnancy. She had macroprolactinoma with suprasella extention. The complications were effectively treated with bromocriptine. It is concluded that pregnancy is considerably safe in most hyperprolactinemic patient treated with bromocriptine or lisuride. As soon as pregnancy is diagnosed the medication should be discontinued. Tumor complication during pregnancy is infrequent in women with functional hyperprolactinemia and in women with microprolactinoma. Patient with macroprolactinoma and suprasella extention, however, have a high risk of complication during pregnancy. Thus, tumor size should be reduced either by surgery and/or medication before allowing the patient to become pregnant. The rare tumor complication occurring during pregnancy is usually treated effectively by the reinstitution of a prolactin inhibiting agent. (Thai J Obstet Gynaecol 1989;1:115-22.)*

Key words : clinical course, outcome of pregnancy, hyperprolactinemia

Hyperprolactinemia is a common cause of secondary amenorrhea and anovulatory infertility[1, 2]. The major cause of hyperprolactinemia is pituitary adenoma secreting prolactin (prolactinoma). Since the assay of serum prolactin and several prolactin inhibiting agents have become available, the treatment of these patients has been effective in most cases. The ovulatory and pregnancy rates are high during the medical treatment[3]. Prolactinoma, however, causes

concern to both the patients and obstetricians as its enlargement during pregnancy may be rapid, thus, resulting in tumor complications such as headache and visual field defect. Previously it was advocated that such patients should be treated with either surgery or radiotherapy before attempting to conceive[4-6]. Experiences gained during the last decade have shown that neither surgery nor radiotherapy provides a definite cure for most infertile women with prolactinoma[7]. At present, most authorities are of the opinion that medical treatment is suitable for most infertile patients with hyperprolactinemia including those who have prolactinomas[8, 9].

The purpose of this study was to determine the clinical course and outcome of pregnancies in hyperprolactinemic women treated with prolactin inhibiting agents at Ramathibodi Hospital.

Materials and Methods

Since 1983 bromocriptine has been used to treat infertile women with hyperprolactinemia attending the Gynaecologic Endocrinology clinic at Ramathibodi Hospital. From 1988 lisuride, another prolactin inhibiting agent, has also been used as an alternative. From 1983 to 1988 fifty-two patients, aged 20 to 36 years with hyperprolactinemia were treated with prolactin inhibiting agents, forty cases were treated with bromocriptine and the other twelve with lisuride. Eighteen from 40 and 5 from 12 patients in the bromocriptine and lisuride groups desired pregnancy. Bromocriptine and lisuride treatment resulted in 16 pregnancies in 13 patients and 2 pregnancies in 2 patients respectively. The clinical course and outcome of these 18 pregnancies were determined.

Results

The clinical characteristics of these patients are shown in Table 1. All but two patients presented with amenorrhea and galactorrhea. Two patients had amenorrhea without galactorrhea. Pretreatment serum prolactin levels varied from 80 to 700 ng/ml. Radiological studies revealed microprolactinoma in 7 patients and macroprolactinoma with suprasella extention in one patient. Normal radiological findings were found in 7 patients. Before pregnancy 13 patients were treated with bromocriptine and the other two were treated with lisuride. Two patients in the bromocriptine group had pituitary surgery previously. The medication was discontinued immediately after pregnancy was confirmed. The patients were informed of the risk of pituitary enlargement during pregnancy and the symptoms and signs of such a complication. Regular antenatal care was provided. Tumor complications such as headache and visual problems were noted during every antenatal visit. Those who had complaints were sent to the opthalmologic clinic for visual field determination.

Summary of the outcome of pregnancies is shown in Table 2. Twelve full term and one preterm pregnancies resulted in viable newborns. No multiple

Table 1 Patients' clinical characteristics

No.	Age	Symptom	Pretreatment prolactin (ng/ml)	Radiological finding	Treatment before pregnancy	Outcome of pregnancy	Tumor complication
1	22	A-G	200	microadenoma	bromocriptine*	induced abortion	no
2.1	26	A-G	165	microadenoma	bromocriptine*	normal full term	no
2.2	31	A-G	56	microadenoma	bromocriptine*	normal full term	no
3	20	A-G	96	normal	bromocriptine	normal full term	severe headache +
4	29	A-G	144	microadenoma	bromocriptine	normal full term	no
5.1	32	A-G	120	microadenoma	bromocriptine	normal full term	no
5.2	34	A-G	80	microadenoma	bromocriptine	spontaneous abortion	no
6.1	26	A-G	700	macroadenoma with suprasella extention	bromocriptine	dead fetus in utero at 28 weeks	severe headache+
6.2	27	A-G	150	microadenoma	bromocriptine	preterm delivery at 35 week	severe headache and bitemporal hemianopia
7	34	A-G	400	microadenoma	bromocriptine	normal full term	no
8	35	A-G	120	normal	bromocriptine	induced abortion	no
9	30	A-G	350	normal	bromocriptine	normal full term	no
10	28	A	57	normal	bromocriptine	normal full term	no
11	30	A	90	normal	bromocriptine	normal full term	no
12	24	A-G	443	normal	bromocriptine	normal full term	no
13	31	A-G	76	normal	bromocriptine	ectopic pregnancy	no
14	26	A-G	152	microadenoma	lisuride	normal full term	no
15	36	A-G	109	microadenoma	lisuride	normal full term	no

* previous pituitary surgery
+ reinstitution of bromocriptine
A = Amenorrhea
A-G = Amenorrhea with galactorrhea

Table 2 Summary of the outcome of pregnancies

Outcome	No.	per cent
Total pregnancies	18	100
Normal full term	12	66.7
Induced abortion	2	11.1
Spontaneous abortion	1	5.5
Ectopic pregnancy	1	5.5
Dead fetus in utero	1	5.5
Preterm delivery	1	5.5

pregnancy occured. Tumor complications during pregnancies were recorded during three pregnancies in two patients (Table 1). One patient with microadenoma had severe headache. The symptom rapidly disappeared after bromocriptine therapy. The other patient with macroprolactinoma and suprasella extention had two pregnancies. During her first pregnancy, she developed severe headache which was relieved by bromocriptine. Unfortunately, the fetus died in utero at 28 weeks of gestation from unknown cause. One year later she became pregnant again. Severe headache and visual field defect (bitemporal hemianopia) occured from 24 weeks of gestation. She was treated with bromocriptine 7.5 mg/day. Headache was relieved and visual field defect did not deteriorate. She delivered a healthy newborn spontaneously at 35 weeks of gestation. The visual impairment had completely disappeared at postpartal check up 6 weeks after delivery. Most patients could breast-fed their infants normally.

Discussion

The clinical course and outcome of most pregnancies in hyperprolactinemic women treated with prolactin inhibiting agents at our clinic is satisfactory. Our results confirm other previous study[9]. One of the concerns while treating hyperprolactinemic infertile women with prolactin inhibiting agents is the outcome of pregnancy. Since the medication is generally continued until pregnancy is diagnosed, every patient thus receives the drug during early gestation. Information gathered during the last fifteen years has assured the both bromocriptine and lisuride treatment are safe. Abortion, multiple pregnancy and fetal malformation were similar to the general population[10, 11]. Postnatal development was also normal[12, 13]. However, for general precaution the medical treatment should be discontinued as soon as pregnancy is diagnosed. Only when tumor complications occur, should prolactin lowering agent such as bromocriptine be reinstituted.

In this study, tumor complications occurred during 3 pregnancies. The course of pregnancies in patients with microprolactinoma and functional hyperprolactinemia is considerably safe. Severe headache occured only in one patient with microprolactinoma and was rapidly relieved by bromocriptine. Patients with macroprolactinoma and suprasella extention, however, developed tumor complications in both pregnancies. High risk of tumor complications is high in patients who have a large tumor extending outside the sella turcica.

In 1979, Gemzell and Wang[5] reviewed the outcome of pregnancies in

women with pituitary adenoma. They found tumor complications occurring during pregnancy in 5 per cent of patients with microprolactinoma and 25 per cent with macroprolactinoma. Since this figure of tumor complication was rather high, they advocated that these patients should have been treated with surgery and/or radiotherapy before attempting to conceive. It was interesting to note that most of these patients had no biochemical evidence of hyperprolactinemia. They were treated with ovulation inducing agents other than bromocriptine. The compilation of data from 1980 to 1984 has shown contradictory results[9]. Of 488 term pregnancies in 430 hyperprolactinemic patients (285 had prolactinoma), only 11 (2.2 per cent) had tumor complications during pregnancy. Ten (2 per cent) had a visual complication and one had diabetes insipidus. At present, most authors are of the opinion that hyperprolactinemic infertile women with microprolactinoma and macroprolactinoma without suprasella extention can effectively be treated with dopamine agonists without prior surgery[7]. Cases of macroprolactinoma with extrasella extention tumor should be treated either by surgery or medication or both. Tumor size should be reduced and confined only in the sella turcica before allowing the patient to become pregnant.

From review of the literature, most of the patients who had tumor complications could effectively be treated with bromocriptine[14-19]. Surgery was performed in a few cases[9]. If pregnancy is near term, induction of labor is advocated[20]. Tumor complications rapidly disappeared after delivery. Due to the low incidence of tumor complications and the availability of effective treatment should such complications occur, we thus accepted the policy of medical treatment of women with hyperprolactinemia including those with prolactinomas without prior surgery. Pituitary surgery requires an experienced surgeon. In unskilled hands, incomplete resection of tumor or damage to adjacent pituitary cells is frequent. Postoperative persistence of elevated prolactin levels or panhypopituitarism may follow. Thus, further treatment will be more complicated. Even in cases of adequate tumor resection, long term follow up has shown a high recurrence rate after surgery[21]. Therefore, medical therapy appears to be appropriate as a primary treatment in almost all hyperprolactinemic infertile patients.

Antenatal care of hyperprolactinemic patients is more or less the same as for general pregnancy. Prolactin lowering agents should be discontinued as soon as pregnancy is diagnosed. Prophylactic medical treatment has been recommended in early studies[22-24]. Today, this practice is no longer advocated because of the low incidence of tumor complications during pregnancy and the availability of effective medical treatment if such complications occur as discussed earlier.

In our opinion, visual field determination may not be necessary in every antenatal visit especially in women with functional hyperprolactinemia and patients with microprolactinoma. Careful

advice to the patients about the risk, signs and symptoms of tumor complications should be done. Finger test performed by an obstetrician or midwives at each antenatal visit may be adequate for screening of visual impairment in patients with no complaint. Only those who had headache or visual symptom were subjected for visual field determination. This policy will cause less interference in busy opthalmologic clinics. During pregnancy some authorities suggested periodic serum prolactin determination[5, 22, 25]. However, the clinical value of this practice has not been proven. The maternal prolactin levels seem not to be predictive of any tumor complications[20, 25, 26]. It also causes a lot of expense. We, therefore, do not follow serum prolactin levels during pregnancy.

In the past, breast feeding was also a controversial issue. During eary postpartum, suckling has a marked stimulatory effect on prolactin secretion[27]. This physiological effect caused concern and some authors advised against breast feeding especially in patients with prolactinomas[28, 29]. Experience gained from later studies revealed that breast feeding does not cause deteriorious effect on prolactinoma[9, 20]. There is therefore, no reason to withhold the patient from the advantages of breast feeding. Most of our patients could breast feed normally.

Summary

In conclusion, this study supports the policy of medical treatment of hyperprolactinemic infertile women without prior surgery and/or radiotherapy except in patients who had a large prolactinoma with suprasella extension. After pregnancy is confirmed the drug should be discontinued. The patients should be carefully informed about the risk, symptoms and signs of tumor complications that might occur during pregnancy. Regular antenatal visits should be performed as usual. Should tumor complications occur, reinstitution of prolactin lowering agent is usually effective. Surgery is limited to those who fail medical treatment. Induction of labor may be considered if pregnancy is near term. After delivery, the patient should be advised to breast feed like other mothers.

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Prevention of Vertical Transmission of Hepatitis B Virus A Randomized Clinical Trial and A Cost - Effectiveness Analysis

Pisake Lumbiganon MD,*
Yupa Urwijitaroon MSc,**
Pensri Kowsuwan MD,+
Pagakrong Lumbiganon MD,+
Manat Panamonta MD, +
Tassanee Sookpranee MD.+

* *Department of Obstetrics and Gynaecology*
\+ *Department of Pediatrics*
** *Blood Bank Center*
Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

Abstract : *A randomized clinical trial and economic analysis was conducted to assess the cost-effectiveness of combined and active immunization for prevention of vertical transmission of hepatitis B virus in high risk newborns (mothers with + HBsAg and + HBeAg). Eighty newborns whose mothers had positive HBsAg and HBeAg were randomized into either combined or only active immunization. These newborns were followed up for 1 year for HBsAg and HBeAg using ELISA technique. The rates of protection of vertical transmission of HBV by combined and active immunization alone were 91.9 and 84.2 per cent respectively. There was no statistically significant difference between the 2 regimens. The cost for prevention of one case of vertival transmission of HBV was 714 baht for vaccine alone and 1847 baht for combined immunization. Combined immunization should be as cost-effective as active immunization only if the cost of HBIG is less than 57 baht or the effectiveness of the vaccine alone regimen is less than 30 per cent.*

Although combined immunization offers the most effective measure for prevention of vertical transmission of HBV. Immunization by vaccine alone is much more cost-effective and should be used for mass immunization. (Thai J Obstet Gynaecol 1989;1:123-7.)

Keywords : vertical transmission, hepatitis B virus, randomized clinical trial, cost-effectiveness analysis

Hapatitis B virus (HBV) infection is endemic in Southeast Asia and tropical Africa[1]. Chronic carriers of HBsAg are at high risk of chronic persistent hepatitis, chronic active hepatitis and primary hepatocellular carcinoma[2-4]. In countries where HBV is endemic, transmission from carrier mothers to their infants has

been estimated to be the cause of about 20 to 40 per cent of all chronic HBV carriers[5]. Such transmission might account for as many as 50 million chronic HBV carriers throughout the world. In addition, chronic HBV carriers serve as a continuing source of infection for others. Thus, prevention of the vertical transmission of HBV should be one of the top priorities in the control and prevention of HBV infection and its associated sequeles.

The most important factor determining whether or not a mother will infect her child is the presence or absence of hepatitis B e-antigen (HBeAg)[6, 7]. HBsAg carrier mothers who were also HBeAg positive infected more than 90 per cent of their infants and most of these infants also became chronic carriers[7]. So, infants born to mothers with positive both HBsAg and HBeAg are at the highest risk of becoming HBsAg carriers.

Hepatitis B immunoglobulin (HBIG) alone or in combination with hepatitis B vaccine has been shown to be effective in the interruption of vertical transmission of hepatitis B virus[8-13]. Passive-active immunization by HBIG and hepatitis B vaccine seems to be the most effective method but it represents a tremendous increase in cost. Four doses of hepatitis B vaccine alone at birth, one month, two months and six months has been shown in a randomized clinical trial to be effective in prevention of HBsAg carrier state in newborn infants of mothers who are chronic carriers of HBsAg and HBeAg. The degree of protection of vaccine alone was not significantly less than those who received HBIG plus vaccine[11]. This might be explained by the small number of subjects in each study group. In Thailand the carrier rates of HBsAg have been reported to be 8 to 10 per cent[14, 15]. If hepatitis B vaccine alone can prevent vertical transmission of HBsAg as effectively as passive-active immunization by HBIG and hepatitis B vaccine, it should be the most cost-efective method. We, therefore, conducted a randomized clinical trial to assess the effectiveness of three doses of hepatitis B vaccine compared to hepatitis B vaccine in combination with HBIG in prevention of vertical transmission of HBV. A cost-effectiveness analysis was carried out using the data from the randomized clinical trial.

Materials and Methods

Starting from January 2, 1985, all pregnant women who attended the antenatal clinic, Srinagarind Hospital, Khon Kaen University were screened for HBsAg in their sera, using the reverse passive hemagglutination (RPHA) technique. Sera from HBsAg pregnant women carriers were further tested for HBeAg, also by RPHA technique. These pregnant women with positive HBsAg and HBeAg were invited for an interview by the principal investigator. The risk of vertical transmission of HBV and the design of the study were explained to them. Special well-baby care was provided for their infants by the pediatricians. Written informed consent was obtained from each mother. Infants born

to these mothers were randomized into the vaccine and vaccine in combination with HBIG groups, (40 for each group). Infants in the vaccine group received 3 doses of hepatitis B vaccine (H-B VAX® containing 10 mcg per 0.5 ml) within 24 hours after birth, at 1 and 6 months of age. Infants in the combination group received 1 ml of HBIG (Hyperhep® containing 200 IU of anti-HBs per ml) within 24 hours after birth and 3 doses of vaccine at the corresponding time with the vaccine group. The vaccine was given intramuscularly in the anterolateral thigh. HBIG was injected separately in the other thigh. Infants of both groups were screened for HBsAg at birth, 1 month, two months, four months and six months by RPHA technique using two capillary tubes of blood and at one year of age by ELISA technique, Fig. 1. One week prior to the appointment date, memoranda was mailed to remind each mother. If the mothers and their infants did not show up on the appointment date, a second memorandum was sent to ask them to come the following week. If they did not show up at the next appointment schedule, the research assistant visited them, collected the infant's sera and made an appointment for the next visit if the mothers wanted to continue participating in the study.

Results

The prevalence of HBsAg among pregnant women who attended the antenatal clinic at Srinagarind Hospital was

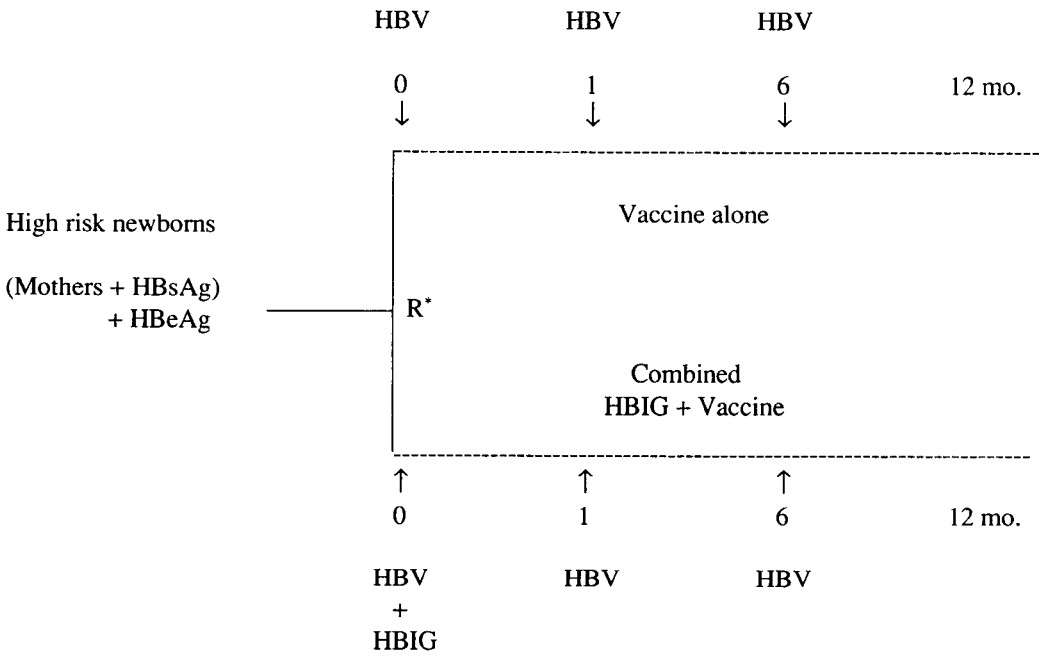

Fig. 1 Immunization schedule of both regimens
R* = Randomization

6 per cent. About one-third of these women also had positive HBeAg. Thirty-eight of forty infants in the vaccine alone group completed the one-year follow up schedule, while 37 of 40 infants in the combined group completed the same one year follow up schedule. The effectiveness of vaccine alone and combined vaccine and HBIG in preventing the vertical transmission of hepatitis B virus was 84.2 and 91.9 per cent respectively. The difference was not statistically significant (p=0.25, Fisher's Exact Test), Table 1. The cost for protection of one case of vertical transmission of HBV by vaccine alone regimen was 714 baht, while that of combined regimen was 1847 baht (US$ 1=25 baht), Table 2. The marginal cost, i.e. the cost for obtaining better prevention by adding HBIG to vaccine alone regimen was 13750 baht per one addition case prevention, Table 3.

Table 1 Effectiveness of immunization regimens

Regimen	Effectiveness* (95% CI)
Vaccine alone	32/38 = 84% (73-96)
Combined HBIG and Vaccine	34/37 = 92% (91-101)

P =0.25, Fisher's Exact Test
* Effectiveness = Negative HBsAg at 12th month

Table 2 Cost-effectiveness of immunization regimen

Analysis	Vaccine alone regimen	Combined regimen
Cost per case*	600	1700
Effectiveness	84 %	92 %
Cost per one case protection	714 (600 -0.84)	1847 (1700 - 0.92)

* 1 dose of vaccine = 200 baht
1 dose of HBIG = 1100 baht

Table 3 Marginal cost

Cost of combined immunization per 100 cases	=	170000 B
Cost of vaccine alone immunization per 100 cases	=	60000 B
Additional cost for combined immunization per 100 cases	=	110000 B
Number of cases prevented by combined regimen (Effectiveness 92%)	=	92
Number of cases prevented by vaccine alone regimen (Effectiveness = 84%)	=	84
- number of addition cases prevented	=	8
- additional cost for one addition case prevented (Marginal cost)	=	110000-8 13750 B

Discussion

This study confirmed the findings that the combined HBIG and vaccine regimen is the most effective regimen in preventing vertical transmission of hepatitis B virus. Hepatitis B vaccine alone regimen is also very effective. Although the combined regimen is more effective, the difference was not statistically significant. This study had an 80 per cent power in detecting 30 per cent difference given α-ereor = 0.05, β-error = 0.2 [14]. By economic analysis, the vaccine alone is much more cost-effective and should be recommended for mass immunization. Sensitivity analysis revealed that combined immunization would be as cost-effective as vaccine alone only if the cost of HBIG is less than 57 baht per

dose or the effectiveness of the vaccine alone regimen is less than 30 per cent which is very unlikely.

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Male Sexual Activity During Pregnancy

Sompol Pongthai MD, MPH.

Department of Obstetrics and Gynaecology,
Faculty of Medicine, Ramathibodi Hospital,
Mahidol University, Bangkok 10400, Thailand

Abstract : *Female sexual desire and activity decreases as pregnancy advances. Little is known about the influence of pregnancy on male sexuality. This study is aimed at establishing sexual activity of husbands during their wives' pregnancy period. Questionnaires were voluntarily completed by the men whose wives had recently given birth during August and September 1982 at Ramathibodi Hospital. There were 279 men who participated. The decrease of sexual desire was markedly observed as pregnancy advanced though it remained unchanged among most men during the first and second trimester. Coital abstinence was increased toward term. Self-masturbation, wet dream and masturbation performed by their wives were significantly increased whereas coitus with prostitutes was significantly reduced. Coitus with other partners and performing masturbation for their wives remained unchanged. These findings show that pregnancy had an influence on the male partner on both sexual desire and sexual activity. (Thai J Obstet Gynaecol 1989 ; 1 : 129-32.)*

Key words : male sexuality, pregnancy

Pregnancy had multiple effects on women both physically as well as psychologically. Sexual desire and sexual activity were decreased as pregnancy advanced[1, 2]. Sexual factors were suggested on the reasons for this decline such as physical discomfort, lack of attractiveness, fear of injuring the unborn child and advice received from the physician[3, 4]. Some psychological effects on the men were also recognized during pregnancy : hypochondriac type disorders or acute psychotic states[5, 6]. Little is known about sexual activity of the male sexual partner of the pregnant woman[7].

It is believed that some change of sexual behaviour would also occur among the men during this period, so this study aimed to establish the man's sexual desire and sexual activity during pregnancy.

Meterials and Methods

Between August and September 1982, questionnaires on personal characteristics and sexual desire as well as sexual activity during one year prior to pregnancy and during pregnancy were

given to the men whose wives had recently given birth and admitted to one of the peurperal wards in the Department of Obstetrics and Gynaecology, Ramathibodi Hospital. The questionnaires were voluntarily completed individually and then returned with anonymity. Proportion of those who had activity was reported as percentage of the whole after omitting the incompleted answer. Comparison of sexual desire and sexual activity was made between the one-year period prior to pregnancy and during pregnancy by *chi-square* test with determination of significance at $p < 0.05$.

Results

There were 279 men who voluntarily participated in this study (approximately 50 per cent of those distributed). Some sociobiologic characteristics were : mean age ± 1 SD was 30.9 ± 5.3 years (range 19-55 years with 50 per cent was between 30-39 years) ; educational level was 24.9 per cent primary school, 25.2 per cent secondary school, 26.4 per cent professional school, 23.1 per cent university ; religion was 95 per cent Buddhism. For their wives : mean age ± 1 SD was 27.6 ± 4.5 years (range 17-42 years with 68.2 per cent was between 20-29 years); educational level was 35.7 per cent primary school, 19.6 per cent secondary school, 28.0 per cent professional school, 16.5 per cent university ; religion was 93.9 per cent Buddhism. More than half of the pregnancies were first gravida (51.9 per cent)

Sexual desire

Table 1 indicates that sexual desire of most men remained unchanged during the first and second trimester (66.78 per cent and 56.43 per cent respectively). During the last trimester, most (59.77 per cent) had decreased sexual desire. This reduction was significantly observed as pregnancy advanced.

Table 1 Male sexual desire during each trimester of pregnancy as compared to the one-year period prior to pregnancy

Period of pregnancy	Sexual desire		
	increase	unalter	decrease
1st trimester (n = 274)	13 (4.74%)	274 (66.78%)	78 (28.46%)
2nd trimester (n = 264)	7 (2.65%)	149 (56.43%)	108 (40.9%)
3rd trimester (n = 266)	12 (4.51%)	95 (35.71%)	159 (59.77%)

Sexual activity

As shown in Table 2, during one-year prior to pregnancy, all had coitus with their wives, 13.5 per cent had extramarital coitus (another partner), 35.2 per cent had coitus with prostitutes, 33.9 per cent masturbated, 14.7 per cent were masturbated by their wives, 10.72 percent maturbated their wives, 25.9 per cent had wet dream and 0.4 per cent had homosexual contact. These activities were changed significantly during pregnancy. Masturbation, masturbation performed by their wives and wet dreams were significantly increased. Coitus with prostitutes was significantly decreased. Coitus with another partner and performing masturbation for their wives remained unchanged. Those who had

Table 2 Comparison of male sexual outlets between one-year period prior to pregnancy and during pregnancy

Sexual outlet	Time		P*
	Prior to pregnancy	During pregnancy	
Wet dream	25.9% (69/266)	33.9% (84/248)	S
Masturbation	33.9% (87/257)	43.2% (105/243)	S
Masturbation by wives	14.7% (38/258)	24.1% (59/245)	S
Masturbation to wives	10.7% (28/261)	15.5% (40/258)	NS
Coitus with wives	100% (279/279)	97.1% (268/276)	NS
Coitus with prostitutes	35.2% (86/244)	26.4% (65/246)	S
Coitus with ex-partners	13.5% (35/260)	15.5% (38/250)	NS
Homosexual	0.4% (1/263)	0.5% (1/242)	NS

* S = Significant
NS = Not Significant

coital abstinence throughout pregnancy was 2.9 per cent.

As shown is Table 3, the performance of each sexual outlet between each trimester was significantly different. Masturbation, coitus with prostitute, coitus with another partner increased as pregnancy advanced while coitus with their wives, masturbation performed by their wives and performing masturbation for their wives decreased. Erotic dream was also increased with high proportion during second trimester. There was one case who reported homosexual contact.

Discussion

This study was carried out at the Department of Obstetrics and Gynaecology, Ramathibodi Hospital ; husbands of women who had recently given birth received a questionnaire concerning sexuality during pregnancy, of which 279 were voluntarily returned (approximately 50 per cent of those distributed). It is appreciated that having taken into account the methodology, this sample cannot be considered representative of the population who delivered at Ramathibodi Hospital nor the population who delivered during the period of study. However, the data provides information of the study group.

There is some change in male sexual desire during pregnancy as generally found among females[2, 7]. The

Table 3 Distribution of male sexual outlets over each trimester of pregnancy

Sexual outlet	Trimester			P*
	1st	2nd	3rd	
Wet dream	15.90% (42/264)	24.03% (62/258)	17.14% (42/245)	S
Masturbation	21.31% (52/244)	28.18% (73/259)	36.82% (95/258)	S
Masturbation by wives	15.07% (38/252)	15.23% (39/256)	14.12% (37/262)	S
Masturbation to wives	11.06% (28/253)	10.07% (26/258)	5.42% (14/258)	S
Coitus with wives	95.25% (261/274)	87.5% (231/264)	56.98%(151/265)	S
Coitus with prostitutes	11.95% (30/251)	18.18% (46/253)	19.68% (50/254)	S
Coitus with ex-partners	10.04% (25/249)	11.37% (29/255)	12.35% (31/251)	S
Homosexual	0.38% (1/257)	0.39% (1/255)	0.39% (1/251)	NS

* S = Significant
NS = Not significant

change consists of increased, decreased and unaltered sexual desire as compared to the one-year period prior to this pregnancy. Most men had unaltered sexual desire during first and second trimester. The proportion of those who reported less sexual desire increased as pregnancy advanced to the extent that more than half of the participants reported decreased desire during the third trimester. This finding can clearly demonstrate the influence of pregnancy on declining sexual desire among males as it did among females[2].

In addition to the change of sexual desire, change of the type of sexual activity is also observed. There was a significant increase in the proportion of men who had wet dreams, masturbation and masturbation performed by their wives during the entire pregnancy as compared to the one-year period to pregnancy while coitus with prostitutes was significantly decreased. There was no change of the proportion of extramarital coitus and masturbation given by men to women. These findings suggest that the alternative sexual outlets of men rather than coitus with their wives alone was still practised in marital life and pregnancy does have an influence on the increase of some types of sexual outlets, e.g. masturbation, wet dreams and masturbation performed by their wives. It is interesting to note that coitus with prostitutes was decreased, whereas, there was no change in extramarital coitus.

Sexual activities over a three three-month period during pregnancy showed the concern of men for their wives. Activities which involved their wives as sexual partners such as coitus, masturbation by their wives, masturbation to their wives were decreased significantly as pregnancy proceeded while those without involvement of their wives increased toward term.

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Knowledge, Attitudes and Acceptance of Amniocentesis Clients in Ramathibodi Hospital

Sauwakon Ajjimakorn MD,*
Chalermsri Thanuntaseth MD,*
Mayuree Jirapinyo MD,*
Tongtis Tongyai MD,*
Daoroong Kangwanpong Dr. rer.nat.**

* *Department of Obstetrics and Gynaecology*
** *Department of Pathology*
Faculty of Medicine Ramathibodi Hospital
Mahidol University
Bangkok 10400, Thailand

Abstract : *Ninety-seven amniocentesis clients were surveyed for their knowledge, attitudes and acceptance of amniocentesis. Only 72 clients (74%) responded to the questionnaire. The study showed that knowledge of the clients of A/C were 61%. All accepted the procedure after pre-amniocentesis counseling. Ninety-six per cent had no distrees or mild distress during the procedure. Twenty-six per cent had mild anxiety and 3% had moderate level of anxiety before the procedure. After the procedure 36% had mild degree, 21% moderate and 17% severe degree of anxiety. The anxiety level decreased after the test results to 17% of mild degree, 3% moderate and 5% severe degree of anxiety. All of the respondents who plan to have future pregnancies will accept the procedure again. (Thai J Obstet Gynaecol 1989; 1:133-7.)*

Key words : amniocentesis, knowledge, attitudes, acceptance

Genetic amniocentesis (A/C) has been established at Ramathibodi hospital since 1983. Before establishing the service, we explored the knowledge, attitudes and acceptance of pregnant women toward prenatal diagnosis (PND).[1] Only 19 per cent of them had any knowledge of PND but 91 per cent would accept the PND if they were at risk.

In this report, the knowledge, attitudes and acceptance of amniocentesis were investigated by a retrospective study of a population of women who had previously undergone PND by A/C for various indications (e.g. : advanced maternal age, previous abnormal chromosome infants, etc.). Some of them have now delivered normal healthy infants and some of them were still continuing their pregnancies at the time of

the investigation.

Materials and Methods

The study included 97 women who had undergone amniocentesis at Ramathibodi Hospital from September 1985 to June 1988 for various indications (advanced maternal age, previous abnormal chormosome infants, previous mutiple organ anomaly babies, etc.). A questionnaire consisting of 33 questions was compiled to obtain clients' profile, namely, age, parity, education, socio-economic status and to assess the knowledge, attitudes and acceptance of A/C for PND. A questionnaire was mailed to each client accompanied by a cover letter that requested participation and asking them to return the completed questionnaire. After one month a repeat questionnaire was mailed to the clients who had not returned their first questionnaire.

Responses to questionnaire items were examined and analysed using a microcomputer.

Results

Characteristics of the study population

Of 97 women who were contacted by mail, 72 completed and returned the questionnaire resulting in a response rate of 74 per cent. The mean age of the respondents was 39 years. Ninety-three per cent were Buddhists, 6 per cent were Christians and only one per cent were Muslims. Almost half of the respondents had graduate education (44 per cent) while 22 per cent had primary school education only and 17 per cent had high school and college education respectively. Some general characteristics are shown in Table 1.

Table 1 Characteristics of the respondents (N = 72)

Characteristics (%)			
Age in years		Income (฿)	
< 26	2.8	<1,000	6.9
26-30	15.3	1,001-3,000	15.3
31-35	18.1	3,001-5,000	11.1
36-40	34.7	5,001-10,000	20.8
> 40	29.4	>10,000	45.8
Educations		Parity	
Primary school	22.2	0	30
Secondary and high school	16.7	1	31.4
College	16.7	2	20
Graduate	44.4	>3	18.6
Religions		No. of living children	
Buddhism	93.1	0	22.9
Christian	5.6	1	35.7
Muslim	1.4	2	27.1
		>3	14.3

Knowledge of amniocentesis

Sixty-one per cent of the clients had knowledge of A/C before undergoing the procedure. Forty per cent obtained their information from physicians, 22 per cent from mass media (newspapers, television), 10 per cent from friends or relatives. Eighty-four per cent were advised to have A/C by physicians and 6 per cent by relatives and mass media respectively.

Attitudes and acceptance to amniocentesis

Eighty-eight per cent accepted A/C immediately after the advice. Ninety-

four per cent had preamniocentesis counseling, only 6 per cent did not. Ninety-three per cent knew the reasons for A/C while 6 per cent did not.

The majority of indications for A/C were advanced maternal age (51 per cent), 29 per cent had previous chromosomal abnormality in a child (Table 2).

Table 2 Indications for amniocentesis

Indications	Per cent
Maternal age	51.4
Previous abnormal chromosome	29.2
Previous handicapped child	4.2
X - linked disease	2.8
Other	11.0
No response	1.4
Total	100

The amount of stress and anxiety before, during and after the A/C are shown in Table 3. Seventy-one per cent had no anxiety before the procedure (after counseling) while 26 per cent had mild anxiety. Fifty-four per cent had no stress during the procedure, while 42 per cent and 4 per cent had mild and moderate degree of stress. After the procedure, the numbers and degree of anxiety were increased, 17 per cent had severe degree of anxiety while 21 per cent and 36 per cent had moderate and mild degree of anxiety. Only 25 per cent remained with no anxiety after the procedure. The degree of anxiety decreased after the test results were available. Only 5 per cent had severe degree of anxiety, 3 per cent had moderate and 17 per cent had mild anxiety. Seventy-five per cent had no anxiety after the procedure. Ninety-six per cent thought that their decision-making for A/C was right and eighty-nine per cent of them would accept A/C in next pregnancy (Table 4). The reasons for the acceptance were confidence in the obstetricians' skill and the low risk of the procedure (80 per cent). Nine per cent of non-accepted respondents was because they had completed their families by tubal ligation.

Table 3 Stress and anxiety of A/C clients

Stress and Anxiety	% of Response			
	1(none)	2(mild)	3(mod)	4(Severe)
Anxiety after counseling	71	26	3	-
Stress during the procedure	54	42	4	-
Anxiety after the procedure	25	36	21	17
Anxiety after the results	75	17	3	5

Table 4 Decision making and acceptance of next pregnancy.

	Yes(%)	No(%)	No response
Decision making (right or wrong)	96	1	3
Accepted A/C in future pregnancy	89	9	2

When asked about the period of waiting for results, 44 per cent said it was too long and 56 per cent said it was not.

Attitudes and acceptances after abnormal results

Seventy-four per cent would accept termination of pregnancy when the fetuses were affected whereas 16 per cent would continue their pregnancies and 10 per cent were undecided. Sixty per cent reported having difficulty in making a decision when the abnormali-

ties had been discovered and 35 per cent reported no difficulty.

Discussion

The demographic characteristics of the participants in this study were somewhat different from our previous study[1]. The mean age of this study was 39 years while the previous study was 27 years. This could be explained by the fifty-one per cent of advanced maternal age indication in the study. The educational level was also higher than the previous one, 61 per cent in this study and 31 per cent in the previous study had an educational level higher than high school.

The knowledge of A/C among the respondents had increased from 0 per cent to 61 per cent. This figure was almost the same as the study of Lippman - Hand in 1981 (68 per cent)[2]. The majority of them had learned about A/C from the physicians (41 per cent) and 22 per cent from the mass media (newspapers, television) which showed that health care providers especially physicians and the mass media had shown an increased concern about PND. This will effect the acceptance of the PND service.

Eithty-eight per cent of the participants who were at risk of having an abnormal fetuses accepted PND after first counseling while 91 per cent of pregnant women in our first study had shown acceptance of PND if they were at risk. Seventy-four per cent accepted termination of pregnancy when the fetuses were affected compared with almost the same number of 78 per cent in our first study.

Even though the major indication for A/C in this study was advanced maternal age as in other reports[3,4], the number in this study was only 51 per cent while Marine et al[3] reported 76 per cent and 90 per cent in Robinson's report[4]. The difference in this figure could be explained by the fact that since this new service was introduced to pregnant women who had no idea of both their risks of having abnormal fetus and the PND service, those who had suffered from having an abnormal fetus would accept PND service better than those who had no problems before. After having recognised their risks and the confidence in the procedure, it is anticipated that the indication of advanced maternal age will total 90 per cent of all indications.

The study showed that the anxiety level of the clients was significantly increased after the A/C procedure ($P<0.001$). After the test results had been received the anxiety decreased to almost the same as the anxiety before the procedure and this was the same as previous studies[4-6]. The period of waiting for the test results was the most stressful psychologically for most women[7, 8]. This study confirmed other reports. To reduce this anxious period we have now reduced the mean culture time from 18 days to about 10 days[9].

Half of the A/C clients had no stress during the procedure and half of them had only a mild degree of stress. All except one said their decision to have A/C done was right and they would accept A/C in their future pregnancies.

The reasons for the acceptance were their confidence in the obstetrician's skill in performing the procedure and the low risk of the procedure (80 per cent), good service 5 per cent, and 8 per cent said because they were at risk. The rest of the non-acceptance group were not at risk since they had completed their pregnancies and had had tubal ligation.

In conclusion, the study has shown that there is increased knowledge of A/C among women at risk. There is a need for more information about PND in the form of physician's education, pamphlets and mass media. The attitudes of the A/C clients to the procedure were quite receptive, only 4 per cent had moderate degree of stress to the procedure. The anxiety level of the clients was increased after the procedure and decreased after their test results were available. Almost all of the women who planned to have future pregnancies would accept the A/C procedure again.

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ROCHE THAILAND
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Congenital Clubfoot: Is It the Result of Compression or Moulding in Utero ?

Yuen Tannirandorn MD.

Department of Obstetrics and Gynaecology,
Faculty of Medicine,
Chulalongkorn University,
Chulalongkorn Hospital,
Bangkok 10500, Thailand

Abstract : *Two fetuses with obstructive uropathy had clubfoot diagnosed on ultrasound before 18 weeks of gestation in the presence of normal amniotic fluid volume. Both had normal karyotypes. Oligohydramnios in the presence of obstructive uropathy may merely be associated with, rather than be the cause of clubfoot. Therefore, congenital clubfoot is not always the result of compression or moulding in utero. (Thai J Obstet Gynaecol 1989; 1 : 139-42.)*

Key words : congenital clubfoot, compression, moulding

Clubfoot is a common birth defect with an overall prevalence of 1.2-3 per 1000 live births[1, 2]. Since Parker and Shattock[3] in 1884 and Browne[4] in 1934 made the observation that clubfoot was associated with oligohydramnios and, therefore, caused by intrauterine moulding, many papers have been published supporting this theory[5-8].

Others, however, have suggested the contrary that a regional growth disturbance is the cause of clubfoot[9-11]. The observation of such an abnormality in the absence of oligohydramnios would argue against the importance of amniotic fluid and the compression or moulding in its aetiology.

The author reports bilateral talipes equinovarus in 2 fetuses with obstructive uropathy but normal amniotic fluid volume in whom the limb defect was diagnosed sonographically before the development of oligohydramnios.

Materials and Methods

Two patients with obstructive uropathy were referred between 16-18 weeks gestation. Scans were performed using an Acuson 128 (Acuson, Mountain View, California), with a 5.0 MHz transducer. In both fetuses, ultrasound guided fetal blood sampling was performed for karyotype determination and

urine aspirated from the dilated bladder for measurment of electrolytes.

Amniotic fluid volume was termed normal if at least one pocket of amniotic fluid measuring 3 cm in its vertical diameter was identified[12].

Results

Obstructive uropathy was confirmed in both fetuses by ultrasound signs of dilated bladder, bilateral hydronephrosis and in one of them, dilatation of the urethra (Table 1). Clubfoot was diagnosed in both cases (Fig. 1). The volume of amniotic fluid was normal in all. Karyotypes were normal in both fetuses. Urine electrolytes were suggestive of some residual renal function[13].

Fig. 1 Ultrasound showing clubfoot at 18 weeks gestation with normal amniotic fluid volume

One patient elected to undergo termination, while the other pregnancy ended in spontaneous abortion. Postmortem findings confirmed obstructive uropathy and bilateral clubfeet in both fetuses (Fig. 2).

Table 1 Clinical, ultrasound and pathology correlations

AGE	PARITY	GA (wk)	ULTRASOUND FINDINGS	AMNIOTIC FLUID VOLUME	KARYOTYPE	OUTCOME	PATHOLOGY
38	G1P0	18	Distended bladder Massive dilatation of penis, Megalourethra, *Bilateral clubfeet*	*Normal*	46, XY	Termination of pregnancy	Prune Belly syndrome, *Bilateral talipes*
27	G1P0	16	Huge dilated bladder, Bilateral hydronehrosis, *Bilateral clubfeet*	*Normal* Oligohydramnios (1 week later)	46,XY	Spontaneous abortion	Cystic dilatation of kidneys, Dilated ureters and urethra, *Bilateral talipes*

Fig. 2 Stillborn with bilateral clubfeet at 23 weeks gestation

Discussion

Both of the fetuses reported here had normal karyotypes. Reported incidence of abnormal karyotypes in fetuses with clubfoot ranges from 22-25 per cent[14, 15]. The sonographic detection of potential abnormality of clubfoot is clearly an indication for rapid karyotyping. In a series of 18 cases of talipes diagnosed by ultrasound, all of whom had normal ammiotic fluid, 83 per cent were associated with other abnormalities[14].

In these 2 cases, prenatal diagnosis of clubfoot was made in association with obstructive uropathy in the absence of oligohydramnios. One of the patients developed oligohydramnios the following week. However, they were both at or before 18 weeks gestation, when the contribution of fetal micturition to amniotic fluid is minimal. It has always been assumed that clubfoot, when diagnosed in the presence of oligohydramnios is due to the reduced volume of the amniotic fluid within the uterine cavity, holding the limbs in a fixed position[2-8]. This theory is based both on the association of clubfoot with intrauterine mechanical factors[8, 16, 17], and on the experimental creation of limb anomalies in animal models[18, 19]. The relevance of these latter studies to human idiopathic clubfoot is uncertain. No evidence exists, that mothers of children with clubfoot are selectively exposed to certain drugs or environmental conditions.

On the other hand, Dietz[9] has suggested, based on clinical findings, that the leg and the foot are invariably small in clubfoot, and a regional growth disturbance may be the cause of clubfoot. The more severe the deformity, the greater the reduction in foot and leg size. Even after adequate correction, deformity may recur during the major growing period of the foot. It is believed that clubfoot resulted from delay in the growth of tissues of the posteromedial compared to the anterolateral foot and leg. Other investigators have found a disproportionate amount of type 1 muscle fibres in many posterior and medial muscle groups and in several peroneal muscles[10, 11]. This suggestion that a regional neural abnormality may be present, since muscle fibre type is neurally determined.

Oligohydramnios was clearly not a causative factor in the two cases of clubfoot described here, which were associated with obstructive uropathy. Congenital clubfoot, therefore, is not always the result of compression or moulding in utero. Whether there are neuronal or tropic mechanisms common to both urinary tract and lower limb

abnormalities or not requires further investigation.

Ackowledgement

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SPECIAL ARTICLE

Pathogenesis, Diagnosis and Treatment of Genital Endometriosis

L Mettler

Department of Obstetrics and Gynaecology,
University of Kiel,
West Germany

Endometriosis is a slowly progressive, partly studied disease. Its genetic background is partly clarified but its aetiology still remains totally unclear. According to Philipp and Huber[1] it is a disease where endometrial epithelium and stroma are found at a location to which it does not belong. With more advanced pelviscopic procedures endometriosis is detected more frequently and any relation to sterility can easily be traced[2].

In a way, the pathogenesis of endometriosis depends on the local conditions in the minor pelvis where metaplastic growth of endometrium can be induced by specific factors leading to the transformation of endometriotic epithelium and stroma by continuous growth as well as direct invasion.

Also immunological factors seem to influence the pathogenesis of endometriosis. Characteristics of ectopic endometrium are, like in endometrium, the receptor content in a certain percentage. This facilitates the possibility of endocrine therapy. As the development of endometriosis, however, does not depend simply on the endocrine stimulation but primarily on the degree of differentiation and modulation of endometriosis the described phenomena do not serve as therapy in many cases. Ectopic endometrium shows benign infiltrations, especially where the stroma has a so called "histocytological penetrative function"[3].

Pathogenesis

The current theory complexes of the pathogenesis the mechanisms do not explain, but also do not exclude each other.

1. The metastatic theory = implantation theory (haematogenic or lymphogenic) or the invasion theory = adenomyosis
2. Metaplastic theory
   coelom-epithel = mesothel-theory.

We know that in over 90 per cent of women at the time of menstruation, endometrial tissue is flushed into the peritoneal cavity (retrograde menstruation). An increased migration of monocytes results that differentiate into peritoneal macrophages and take up phagocytotic functions.

The question arises why in some women the contact of endometrium and

peritoneum leads to endometriosis and in others this contact does not provoke any implantation of endometrial tissue on the peritoneum, ovary, etc..

Probably, certain immunological and hormonal conditions facilitate the growth of normal or metaplastically produced endometrium. These are on one side growth factors produced by mesenchymal cells, fibroblasts, macrophages and by hormone-secreting cells. The cell proliferation also depends on receptors that are frequently localised at the cell membrane.

It is known that in endometriotic lesions receptors of progesterone and estrogens can be missing. In a number of endometriosis patients on the other side higher numbers of macrophages were determined in intraabdominal fluid than in non-endometriosis patients. Thus, originated our "Macrophage theory" (Fig. 1).

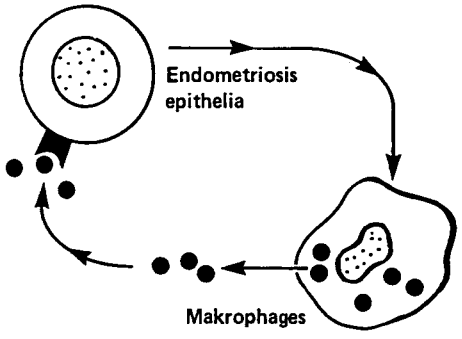


Fig. 1 Schematic presentation of "Makrophage -Hypothesis" for the pathogenesis of endometriosis. Endometrioid tissue enters through retrograde menstruation into the peritoneal cavity and stimulates the migration of makrophages. Growth factors of makrophages (dark points) can stimulate epithelial growth in case a corresponding fms coded receptor is expressed.

In this complex it is thought that certain macrophage populations produce growth factors that promote the growth and proliferation of endometrioid epithelia.

Prerequisites for this theory would be an adequate receptor for macrophages growth factors on the surface of endometriotic epithelia. This receptor is coded by the oncogen "fms" (Fig.2).

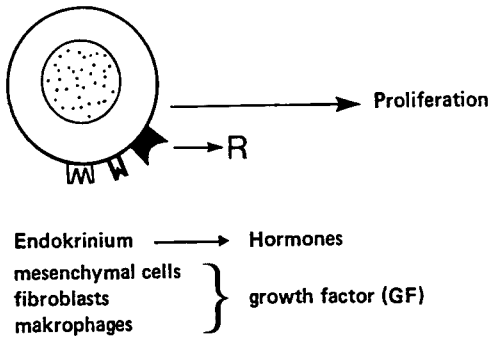


Fig. 2 Schematic presentation of cell varieties that can promote the proliferation of endometrial cells by secretion of hormones or other growth factors (makrophages, fibroblasts). Prerequisite for the efficiency is the expression of corresponding receptors (R) by epithelia.

As each body cell contains the gene, a proof of the corresponding RNA-transcript or of the receptor protein could verify the validity of the theory. At present, we have tried with phosphor labeled "fms" copy probes using the technique of Northernblot analysis to identify corresponding RNA-transcripts.

For a short time we have produced monoclonal antibodies recognizing the receptor protein for macrophage growth factor. In this process in a vicious circle

(Fig.3) endometriotic foci stimulate macrophage migration into the peritoneal cavity. Macrophages themselves produce growth-factors that possibly favour the proliferation of endometriotic epithelia.

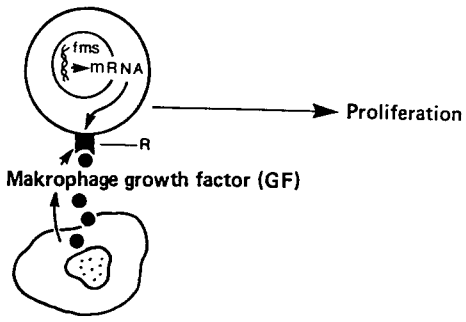


Fig. 3 Scheme for the "Makrophage - Hypothesis" of endometriosis. Dystrophic endometrium provokes the migration of makrophages into the peritoneal cavity, who on the other side secrete growth factors (GF) for the proliferation of endometrioid epithelia. Prerequisite for the efficiency is the expression of a corresponding receptor through epithelia. The specific receptor for makrophages growth is the onkoprotein of the onk-gene fms.

Diagnosis

Endometriosis has a distinct morphology where macroscopically the bloody content of different sized ovarian cysts represent a characteristic sign at pelviscopy or laparotomy. Histologically, the full picture of endometrium is seldom developed. In characteristic cases one sees a small, moderately proliferated endometrium with mucous glands and stroma. Fully secretory developed cells are lacking. In a cytokeratin-stain, epithelia are visible. The dystopic endometrium does not posess the full endocrine activity. In about 30 per cent hormonal receptors are not found. The surrounding stroma contains endometrioid stroma cells.

Is it at all necessary to treat endometriosis at an early stage? Is it really a disease? For the sake of saving a woman from having continuous dysmenorrhea durring her reproductive age it seems necessary to diagnose her early, treat her early and prevent advanced disease.

Diagnostically the following points may be considered :

1. Pains
2. Palpation
3. Speculum presentation
4. Ultrasound diagnosis
5. Pelviscopy with a direct visualisation of foci
6. Histology
7. Success after symptomatic treatment
8. Classification

Pains as symptoms

Dysmenorrhea is the leading symptom of endometriosis. It is found in uterine as well as in extrauterine localisation. Dysmenorrhea carries significant social medical aspects. It belongs in the life of many young women and has always been tolerated as destiny. It still disturbs the life quality of many females for a few days every month. An account of pains in a woman with endometriosis and dysmenorrhoea caused in 34 years during the reproductive period for 5 days every month results in 5

1/2 years of having to tolerate pain. Other symptoms are dyspareunia and chronic abdominal pain. In patients with endometriosis we found 65 per cent pain as a symptom and 35 per cent with no pain. Early diagnosis and treatment seems reasonable.

Palpation

The classic bimanual palpation in endometriosis patients is found negative in 60 per cent of endometriotic patients. Besides the rectal investigation it is the rectovaginal investigation that allows us to diagnose endometriotic conditions.

Speculum presentation

The visualisation of the cervix and the anterior vaginal wall with the duck-mouth speculum allows the localisation of endometriotic foci on the cervix. With endocoagulation at endometriotic foci a correlation with black coloration is seen (Thermocolor-test)[2].

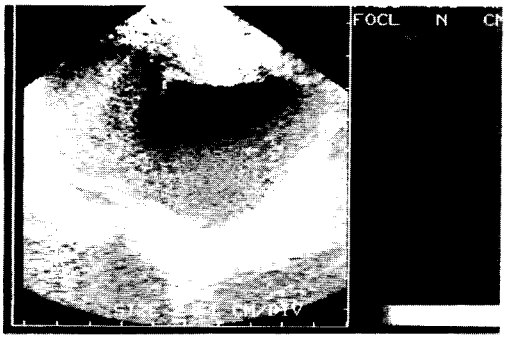


Fig. 4 Vaginosonographical scan of an ovarian endometrioma with cloudy structures easy to be differentiated from other ovarian tumours

Ultrasound diagnosis

The vaginosonographical examination gives espeically good information of endometriotic foci in the ovaries with an exact measurement of endometriomas in diameter (Fig. 4).

Pelviscopy

According to anamnesis and the clinical picture, the patients can be divided into 4 groups :

1. young females with pain and later desire to have children
2. females that have completed their reproductive performance having pain
3. sterile patients and
4. females with symptoms as in endometriosis.

Typical symptoms of endomrtriosis are the lack of blood in the pouch of Douglas and the dark coloration of endometriotic foci at the Thermocolor-test where 100-120° C endocoagulation is applied[2]. Even large endometric foci with 30-50 ml menstrual blood in the pouch of Douglas are sometimes not related to pain in the patients. They produce, however, over the years nuclear abdominal discomfort which we understand accounts for 30-50 ml menstrual blood being absorbed continuously. Pelviscopically an interesting distribution of foci can be found :

1. on the peritoneum
2. in the area of sacro-uterine ligaments
3. on the ovary
4. in the ovary (endometrioma,

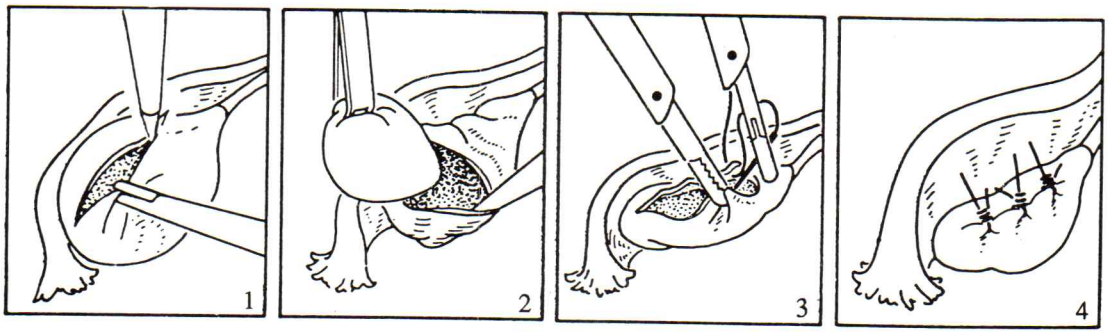


Fig. 5 Ovarian endometrioma presented at operative pelviscopy, consecutive pelviscopic cystpuncture (1), enucleation (2), and adaption of wound margins by endosutures with extracorporal knotting technique (3, 4)

Fig.5)

5. within the uterus = adenomyosis uteri
6. in the tubes (endosalpingitis nodosa)
7. on the bladder roof
8. on the intestines
9. on the spleen
10. on the diaphragm

Histology

As already described, typical endometriotic lesions are small, only slightly proliferated endometrium with some glands and abundant stroma is visible. Figure 6 shows an endometriotic focus in the mesosalpinx in an immune-alkaline phosphate stain of the paraffin section using a monoclonal antibody

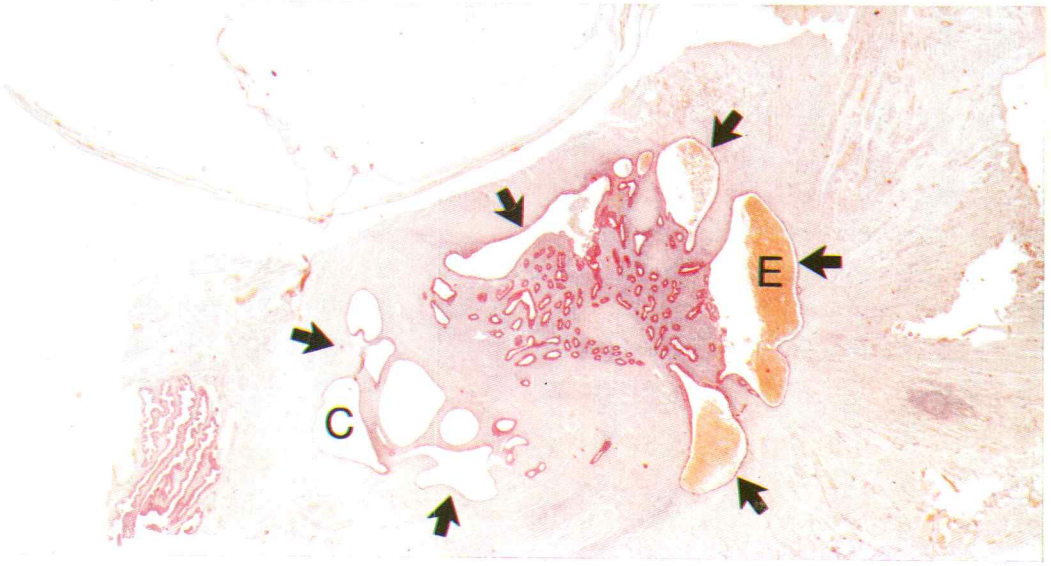


Fig. 6 Immune-histochemical stain of an endometriotic lesion in the Falloppian-tube mesosalpinx. Left: normal tubal mucose. In der endometriotic cysts (C) are many erythrocytes (E). Epithelia are presented in red. 5 µ parffin sections. Immune-alkaline phosphatase reaction with a monoclonal antibody against human epithelia Haemalum-nuclear-counter staining (x 19)

against epithelia. These are selectively shown. The stromal surrounding contains typical endometrial cells, a few haemosiderin carrying macrophages and mononuclear cell. Especially in fresh lesions eosinophilic granulocytes are present. This can be interpreted as a reaction in the sense of an immunological inflammation.

Success after symptomatic treatment

The curative success rate of endocrine treatment with the disappearance of dysmenorrhoea is indicative of the disease.

Classification

The classification is done according to the endoscopic dividing pelvic endometriosis into 3 steps keeping step IV for extragenital endometriosis (Fig.7). The application of the AFS-Scores[4] (American Fertility Society) with a more detailed localisation of the lesions seems only advisible in scientific evaluations. The EEC-classification is identical to the earlier published classification by Acosta[5] and can be directly placed at all operative procedures.

A comparison of the 3 classifications ACOSTA, EEC and AFS is given as follows :

AFS 1-5	= EEC I	= ACOSTA I
AFS 6-15	= EEC II	= ACOSTA II
AFS 16-40	= EEC III	= ACOSTA III
AFS > 40	= EEC IV	= ACOSTA IV

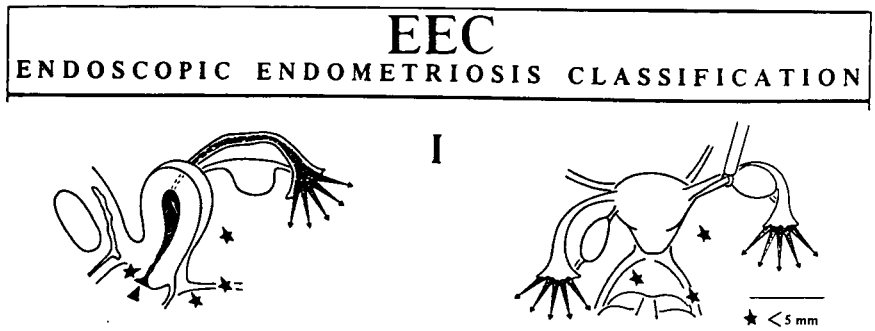
Because of its complexity, the AFS classification is rather difficult for use in routine diagnostic procedures. Endometriosis represents a specific gynaecological disease. The success of treatment depends on good diagnosis as well as application of a combined knowledge of surgery, endocrinology and reproductive biology.

Therapy and Results

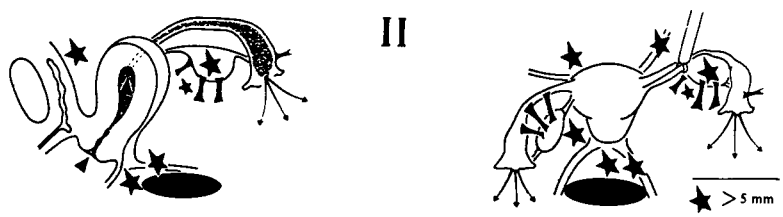
As already stated by many authors the surgical removal of endometriotic foci still represents the optimal therapy. Pure endocrine therapy with application of hormones as lynestrenol, danazol, gestrinone preparation or LH-RH superanalogues over 3-6 months leads to a regression of ectopic foci. Pelviscopically this regression can easily be verified by vanishing or disappeared lesions. Therefore, we advise combined diagnostic, surgical and endocrine treatment in 3 steps :

1. Diagnosis including biopsies and surgical destruction of endometriotic implants as radical as possible,
2. endocrine suppression,
3. second-look pelviscopy with continous surgical treatment by pelviscopy or laparotomy if necessary for example : salpingostomy, cystenucleation, etc..

By surgical treatment pelviscopy is applied. If extensive surgical procedures via pelviscopy are not performable a laparotomy is performed. For the second step we advise one of the following 5 treatment modalities (Table 1).

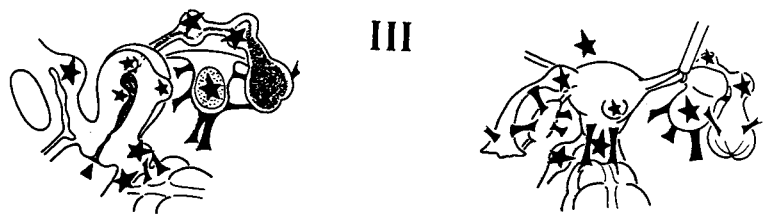


GROUP I endometriosis includes foci located in the lower pelvis (and portio– vaginalis) which do not exceed 5 mm in diameter. Both tubes being completely patent (patency degree I according to FIKENTSCHER and SEMM 1964).

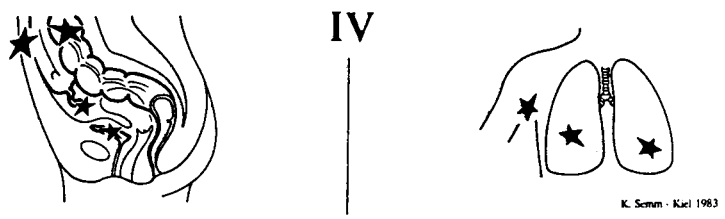


GROUP II endometriosis must be diagnosed (automatically) when
- endometriotic foci are found in the lower pelvis exceeding 5 mm in diameter, free blood is found in the cul–de–sac and spots are demonstrated on the top of the bladder, or when
- periovarian or peritubal adhesions exist or, high–grade ampullar stenosis or phimosis can be observed during ascending chromosalpingoscopy.

Each of these individual findings (in combination with a Group I diagnosis) is classified as Group II.



GROUP III endometriosis must be diagnosed: When in addition adenomyosis in the uterus, especially in the utero–tubal junction, and in the tubes can be observed, or in cases of chocolate cysts, implants in the sacro–uterine ligaments or sactosalpinges.



GROUP IV includes extragenital endometrial implants in the entire abdominal cavity, in the urinary bladder (cystoscopy!), the respiratory system or on the skin.

This optical classification from endometriosis Group I – IV may be supported by biopsy in cases of doubt. The Thermo–Color–Test will give evidence of peritoneal endometriosis.

Fig. 7 Endoscopic endometriosis classification (Semm 1984)

Table 1 Endocrine regulation within the 3-step therapy of genital endometriosis over 3-6 months

Lynestrenol (2 x 5 mg daily)
Danazol (3 x 200 mg daily)
Gestrinone (2 x 2.5 mg weekly)
Buserelin (6 x 150 µg daily)*
Zoladex (3.6 mg monthly)

**As example of LH-RH agonist therapy*

In this paper, I would like to compare a recent group of patients treated in this 3-step therapy with the 5 different endocrine modalities in the second step. Gestrinone, Buserelin and Zoladex were given just in this study, while Danazol and Lynestrenol represent treatment modalities, given for many years, with a significantly higher success rate for the Danazol treated patients[6].

Properties of Danazol - mechanisms of action

Danazol, as a synthetic steroid, is an isoxazole of 17-alpha-ethinyl-testosterone (ethisterone), which is well absorbed by the oral route with a circulating half-life of about 15 hours in humans. At least 60 different metabolites have been identified (one of which is 17-alpha-ethinyl testosterone). Their role in the biological effects of Danazol is still controversial. Danazol has multiple effects at various sites of the female reproductive system which are the direct or indirect consequences of its binding affinity to intracellular steroid receptors and its capacity to inhibit multiple enzymes involved in gonadal and adrenal steroidogenesis.

In addition, the interaction of Danazol with the regulation of the immune system may also contribute to its effects. The effects are respectively a reduced release of GnRH, FSH and LH, at the ovarian level an alteration of normal follicular growth with estrogen and progesterone suppression and a direct suppression of endometrium and endometriotic tissue growth. Danazol reduces liver synthesis of the sex hormone binding globulin (SHBG) and displaces free testosterone from this carrier protein, increasing the levels of the bioavailable testosterone, which will further cause atrophy of the endometrial and endometriotic tissues. This agent by inhibiting ovarian enzymes and steroidogenesis also reduces the production of estrogen.

In comparison to other drugs, Danazol reveals the production of a reversible atrophy of the endometrium. It also interacts directly with intracellular steroid receptors present in endometrium. The binding activity of Danazol is high for AR, lower for PR (3 per cent of progesterone) receptors. The direct androgenic activity of Danazol and the increase of free testosterone due to the effect of SHBG also produces further endometrial atrophy.

It is clear that Danzol therapy induces atrophy and regression of endometrium implants as promptly as after the second month of therapy with cellular inactivity and degeneration. The effects of Danazol are multiple and complex and create a hormonal milieu unfavourable for the growth of endometriotic cells. On eutopic as well as ectopic endometrium it produces a marked regres-

sion of the hormone-dependent endometriotic tissue.

Properties of Gestrinone

Gestrinone is an original steroid intended for use as an oral contraceptive agent administered with one or two doses a week. It has been prepared by total synthesis by Roussel-Uclaf in 1965. The biological spectrum of activities is quite original. In vivo as well as in vitro (receptor binding competition) it has shown marked antiprogestative[7] and antihidatory effects and practically no estrogenic effect[8].

Given at a dosage of 5 mg per week the preparation gestrinone was given in 5000 cycles as a contraceptive to women of child bearing age. The Pearl-index was 4, the tolerance satisfactory.

As the main side effects observed in these clinical contraceptive trials were amenorrhoea, decreased breast size and acne, a significant inhibition of endometrial tissue growth was evident. The endometrium of women on gestrinone became markedly atrophic and suggested its possible use in the treatment of endometriosis.

The properties of gestrinone can be summarized as being anti-estrogenic, anti-progestagenic and antiandrogenic as well as showing pituitary inhibition and an effect on the steroid receptor level of the endometrium[8].

Properties of Buserelin and Zoladex

The LH-RH analogues have a 200 folds more potent action than the native peptide and block receptors on the pituitary and ovarian level. Buserelin (3 x 300 µg D-Ser-(Bu^t) -GnRH was given intranasally daily and Zoladex (3.6 mg D-Ser (Bu^t) -GnRH intracutaneously per month. Table 2 and 3 evaluate a group of patients treated between 1985 and 1988 in respect to the effect of therapy and incidence of pregnancies up to 6 months post treatment. No statistically significant differences were found in the group treated with Danazol, Gestrinone, Buserelin and Zoladex. Although side effects in the GnRH analogue groups especially hot flushes seemed to be increased. The twice weekly medication of Gestrinone was well accepted. GnRH analogues appeared to be comparable treatment modalities and could well be used in unsuccessfully treated endometriosis cases with estrogen and

Table 2 Evaluation of 224 patients prior and after 3-step endometriosis therapy (1985-1988)

	Patients	Prior to therapy					after therapy				
	n	0	I	II	III	IV	0	I	II	III	IV
Gestrinone	30	0	10	10	10	0	22	7	0	1	0
Lynestrenol	33	0	14	9	10	0	16	9	7	1	0
Danazol	31	0	12	12	7	0	17	14	0	0	0
Buserelin	80	0	22	31	17	10	49	24	7	0	0
Zoladex	50	0	20	19	10	1	26	14	8	2	0
Tatal	224	0	78	81	54	11	130	68	22	4	0

Table 3 Evaluation of the incidence of pregnancies for 224 patients after the 3-step treatment of genital endometriosis (1985 - 1988)

	Patients	Pregnacies		Abortions and Tubal pregnancies		Living baby rate	
	n	n	%	n	%	n	%
Gestrinone	30	19	63,2	2	6,6	17	56,6
Lynestrenol	33	10	35,3	1	0,3	9	27, 3
Danazol	31	14	45,2	0	0	14	45,2 (1 x twins)
Buserelin	80	43	54	3	3,75	40	50,0
Zoladex	50	21	42	2	4	15	30,0
Tatal	224	78	35	8	18,6	95	42,4

progesterone receptors in the lesions.

Discussion

According to our study a long term application of gestagens, Danazol, Gestrinone and GnRH-analogues result in cellular inactivity and only partly in cellular desintegration. In peritoneum implants after surgico-medical therapy some remaining endometriotic tissue with an induced atrophy was still found. It seems that peritoneal implants respond better on an endocrine therapy than ovarian implants. All applied drugs create a hormonal milieu unfavourable for the growth of endometriotic cells. Only Danazol, however, acts directly at the tissue level of the endometriotic implants itself. Surgical therapy with excision of lesions should always be performed if possible as the first diagnostic step and be followed by endocrine therapy if pelviscopy is available. If only a laparotomy can verify the diagnosis a hormonal pretreatment at suspicion of endometriosis is suggested.

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