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EDITORIAL

Use of emergency contraceptive pill in adolescents

Every year, unintended pregnancies lead to at least 20 million unsafe abortions and result in the death of some 80,000 women, mostly adolescents around the world. Recently an adolescent client came to our family planning clinic consulting about an unwanted pregnancy. She had sexual intercourse without contraception and subsequently her boy friend gave her one emergency contraceptive pill. Two months later, she missed her period and her urine pregnancy test was positive. Obviously she was quite frightened and did not wish her parents to know about her mishap. Thus she came to the clinic for a request of abortion. This example is quite common in our society. Currently, emergency contraceptive pill is very popular among Thai adolescents. However the correct use of this pill should be of great concern. Most of adolescents think that one progesterone only pill is adequate for preventing pregnancy after sexual intercourse. This misconception results in many unexpected pregnancies and sometimes end up in unsafe abortions and maternal deaths. Conversely excessive and too frequent use of post coital progesterone only pill is also another concern in teenagers who have multiple sex partners.

The Yuzpe regimen for emergency contraception is a useful alternative method for preventing pregnancy. It should be used as soon as possible within 72 hours after unprotected intercourse and taking the second dose 12 hours after the first one. The incorrect use of emergency contraception pill causes the failure of method and leads to the problem of unwanted pregnancies. It is time for us, gynecologists, to educate people about the correct use of emergency contraception and safe sex to prevent the unwanted pregnancies and subsequent social problems.

However we must not overlook the use of condom which is convenient and fairly effective emergency contraception for teenagers. It also has an additional value of preventing STD particularly HIV infection, and plays a significant role in the national AIDS preventing programme. We hope that this editorial comment will make readers awaring of this important adolescent problem.

Assoc. Prof. Surasak Taneepanichskul, MD
Editor

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SPECIAL ARTICLE

Congenital Malformations in Twins

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ABSTRACT

Congenital malformations in twins are found infrequently but not uncommon, its prevalence varies greatly between 0.2 to 18.3 percent. In comparison with singletons, it is found more common in twin than in singleton pregnancy, especially in like-sexed twins. Between monozygotic and dizygotic twins, monozygotic twins are found to increase in prevalence of major and multiple anomalies, but same prevalence for minor anomalies. Main categories are divided into malformations unique and not unique to multiple conception. The first one consists of conjoined twins which is resulted from incomplete separation of a single embryo and acardiac twins which is resulted from vascular interchange theory. Congenital malformations not unique to multiple conception consist of congenital heart disease, positional defects, neural tube defects, GI, KUB anomalies, and chromosome anomalies which are mostly more common in twins. Etiology is not clearly understood, but thought to be a part of twinning process itself, which propose that their etiologic hypotheses are not the same as those in singleton pregnancy. Diagnosis, management, and prognosis are also discussed.

Key words : congenital malformations, twins

Congenital malformations in twins are found infrequently and knowledge about them is not precisely understood. Therefore, some physicians may somewhat not realize with this problem because of these reasons. This article has reviewed from varying issues to summarize its understanding.

Prevalence

Prevalence of congenital malformations in twins vary greatly between studies, ranged from 0.2 to 18.3 percent.[1-5] This variation was due to she differences in study method, including range of anomalies studied, completeness of examination, demographic differences, and chance variation as the number of affected twins studied is rather small.

It is mostly found that prevalence of congenital malformations are more common in twin than in singleton pregnancy, ratio of prevalence rate at birth of anomalies in twins to rate in singleton varies from 1.1 to 3.5.[1-5] There are only few studies contrastly reported the above findings.[5,6]

Within the group of twins , like-sexed twins are found to increase in prevalence of congenital malformations , ratio of prevalence rate at birth of anomalies in twins of like sex to rate in twins of unlike sex varies from 1.1 to 6.6.[1-6] When zygosity has been determined, monozygotic twins are found to increase in prevalence of major and multiple anomalies which are likely to be the result of an insult in early embryonic life, but (defects which occur in later life in utero) there are no different in prevalence of the between both monozygotic and dizygotic twins.[7]

Classification

There is no definite classification for congenital malformations in twins. From reviewing, it is more practical to divide congenital malformations in twins into two categories.

1. Malformations unique to multiple conception

1.1 Conjoined twins

Conjoined twins refers to incomplete anatomic separation of some location bet-ween monozygotic twins causing connection somewhere between two fetuses.[1-9]

1.2 Acardiac twins

Acardiac twins refers to a complex malformation associated with monozygotic, monochorionic twins, in which one twin has a severe abnormality involving malformations of the head, neck, and upper body with absent or rudimentary nonfunctioning heart.[1-9] Acardiac twins may also be called acardiac monster, holoacardius, or chorioangiopagus parasiticus.[1,5,9]

1.3 Fetus-in-fetu

Fetus-in-fetu refers to monozygotic twins which one fetus or parts of a fetus lodges within another fetus, hypothesis is similar to that of an acardiac twins.[1,5]

2. Malformations not unique to multiple conception

2.1 Congenital heart disease, ie, endocardial cushion defect

2.2 Positional defects, ie, talipes, hip dislocation, skull asymmetry

2.3 Neural tube defects, ie, spina bifida, anencephaly, encephalocele

2.4 GI, KUB anomalies, ie, esophageal atresia, TE fistula, cloacal extrophy

2.5 Chromosome anomalies, ie, Turner , Down's, and Klinefelter syndrome

Etiologic hypotheses

Although no definite theory, there are hypotheses about congenital malformations in twins , consists of

1. A part of monozygotic twinning process

1.1. Incomplete separation

Conjoined twins are thought to be an incomplete separation of a single embryo after the formation of two embryonic discs, mostly after 13 days of conception.[7,8] The precise reason for this events has not been established.

1.2. Factors at early embryonic period

It is not clearly understood to explain this theory, but all early embryonic malformations and malformation complexes such as sirenomelia, holoprosencephaly, cloacal extrophy, anencephaly, congenital heart disease, Goldenhar syndrome, de Lange syndrome, and Rubinstein-Taybi syndrome are increased in monozygotic twins. The reason for this association is considered to be the common etiology for both the monozygotic twinning and the early malformation problem.[1,7,8,10] This category is supposed to be the result of interaction between two fetuses, maternal tissues might accept less easily to antigenically different and competing trophoblasts leads to an anomaly of one or two fetuses, neural tube defects is the most typical explanation in this theory and some investigators suggest that there are different in etiology between twin and singleton pregnancy for this group of anomalies.[11,12]

2. Vascular interchange

This etiology results from any vascular interchange between the monozygotic twins. This reason is explained for acardiac twins, amorphous twins, and fetus-in-fetu. Vascular connection between twins leading to reversal of blood flow to one twin, called the twin reversed arterial perfusion (TRAP) sequence, causing one "perfused" and the other "pump" twin. Perfused twin receives unoxygenated blood resulting in aplasia of the heart, head, and upper limbs. The pump twin is usually morphologically normal, or may sometimes have heart failure and hydrops.[1,4,5] This category may also include microcephaly, porencephalic cysts, hydranencephaly, intestinal atresia, aplasia cutis, and limb amputation.[7,8] This vascular interchange theory is exclusively observed in monocho-rionic, especially monoamniotic placentation in monozygotic twins. Monochorionic diamniotic placentation is less common, but also typical.[1,3,7] Dichorionic diamniotic monozygotic twins can be found as rare cases.[13] Moreover, it has also been reported in dizygotic twins

twins. Monochorionic diamniotic placentation is less common, but also typical.[1,3,7] Dichorionic diamniotic monozygotic twins can be found as rare cases.[13] Moreover, it has also been reported in dizygotic twins as a very rare case where the placenta has fused.[14,15]

3. Factors in utero during late gestation

This etiology explains for other malfor-mations that prevalence rate does not differ between monozygotic and dizygotic twins.[6,7] The examples in this category are cleft lip, cleft palate, and other minor anomalies.

4. Limited space

Some positional defects such as talipes, hip dislocation, and skull asymmetry are also more common in twin than in singleton pregnancy, this category is thought to be the consequence of limited growing space and relative restriction of movement, but this fact has not been proven.[7] This twins associated defects are usually resolved quickly and spontaneously, true talipes equinovarus and congenital hip dislocation are more likely from genetic factor.[5]

Noted some common malformations and their points of interest on prevalence and hypotheses are summarized in Table 1.

Diagnosis

1. Clinical examination

Clinical manifestations on the mother vary remarkably. It can be range from high degree of suspicion to normal twin uterus. Marked overdistended uterus is common due to polyhydramnios which can be occurred in acardiac twins, conjoined twins, NTD, and GI malformations. On Leopold's maneuver, some conjoined twins may be found that two fetal heads lie closely and move together to another lie in different time. Twins with discordant or concordant anencephaly may be found that global shaped fetal head is undetected while multiple small parts of the fetuses are palpable. On the other hand, some anomalies such as acardiac twins with just an amorphous mass may produce different clinical entity with small uterus and may mislead as a singleton pregnancy.

2. Maternal serum markers

As generally known, screening on maternal serum markers can assist to assess candidates for prenatal diagnosis, for examples, increased alpha-fetoprotein is found in neural tube defects and decreased alpha-fetoprotein in chromosome anomalies. In twins, serum markers have more diagnostic dilemma according to twins itself which may influence the effects of serum markers level. Upto dates, maternal serum markers in twins are under investigation as aspects of interests.[16,17]

3. Ultrasound

It is recommended that when even multiple gestation are suspected clinically, serial real time ultrasound scans should be obtained beginning in the first trimester,[18] and ultrasound has definitely proved of value in detection of anomalies in twins in the second trimester.[19] Ultrasound findings of conjoined and acardiac twins are shown in Table 2. Ultrasound findings of congenital malformations not unique to twins are alike those of singleton fetuses, so there are not mentioned here.

Table 1. Some common malformations and their prevalence and hypotheses[1-10,12-15,20-23]

	Hypotheses	Prevalence	Inherited pattern	Zygosity, Chorionicity	Sex ratio	Number of sharity
Conjoined Twins	Incomplete Separation of a single embryo after day 13th	1 : 50,000 to 1 : 100,000 births and 1:100 to 1:200 MZ twins	sporadic, and no recurrent risk	MZ only, MC-MA (MZ:monozygotic MC:monochorionic MA:monoamniotic)	like-sex only, F>M (F=75%) (F:female)	concordant
Acardiac Twins	Vascular Connection	1:30,000 to 1:35,000 births and 1:100 in MZ twins	sporadic	MZ a rule, MC a rule, MA>DA, MZ-DC rare, DZ very rare	like-sex a rule, unlike-sex rare, F/M vary	concordant
Congenital Heart disease	Disturbance in laterality of embryo's hemodyna-mic gradient	increase in twins compared with singleton	sporadic, increase recurrent If same environs	MZ>DZ (DZ:dizygotic DC:dichorionic DA:diamniotic)	like-sex> unlike-sex	discordant> concordant, concordant rate=6.8% only
Neural tube Defects (anencephaly encephalo-cele and spina bifida)	contact and interaction between two trophoblasts etiology is thought to be different from those in singletons	1.6:1,000 twin births(1:1,000 in singletons), increase in anencephaly and encepha-locele, but decrease in spina bifida	sporadic, recurrent risk = 8% if next pregnant is twins, and risk= 1-2% if singleton	MZ>DZ	like-sex> unlike-sex, F>M,(F= 55-80%) (F:female M:male)	discordant> concordant, concordant rate=3.7% only
GI,KUB (esophageal atresia,TE-fis-tular,cloacal extrophy)	Twinning reaction in early embryonic period	five-fold increase in twins compared with singleton	sporadic, recurrent rate is low	MZ>DZ	like-sex> unlike-sex	discordant> concordant, concordant rate=5% only
Positional Defects (talipes)	limit space, restriction of movement	increase in twins,but for mild defects	none	variable	variable	variable

Table 2. Ultrasound findings in conjoined and acardiac twins[1-5,9,21]

	Conjoined twins	Acardiac twins
Fetus	Two fetuses lie adjacent to each other and do not move apart with fetal movement. Joining part of the fetuses is visible, most common at the thorax as called thoracopagus. Other joining parts may exist at the head (craniopagus), inferior rump (ischiopagus), posterolateral rump (pygopagus), back above sacrum (rachipagus). Sometimes there may be two heads with one body (dice-phalus),or even two faces with one head and body (diprosopus).	There are two different fetus, one is the normal pump twin, the other is acardiac twin. The acardiac twin get its blood supply from pump twin, it either has no head or anencephaly. Its upper trunk and neck area will be thickened. An omphalocele may be present. Upper limbs are sometime absent. Club feet and absent toes are often seen. No cardiac pulsation. Limb movements are sometimes visible in acardiac fetus. The other twin, so called pump twin, are often normal. It sometimes may show sign of hydrops with hepatosplenomegaly, cardiomegaly, ascites, and pleural effusion.
Amniotic Fluid	Polyhydramnios is common. It can be found up to 75 percent of cases.	Polyhydramnios is common. If two sacs, polyhydramnios is found with pump twin and oligohydramnios with acardiac twin.
Membrane	No membrane	No membrane or sometimes thin membrane
Cord	Usually normal	Single umbilical artery is found 50% of cases
Placenta	Normal	May be enlarged with fetal hydrops
Time detectable	As early as 9 weeks	As early as 12 weeks

Fig. 1. Sonographic finding in conjoined twins, as early as 10 weeks by vaginal probe showing one body with two heads.[26]

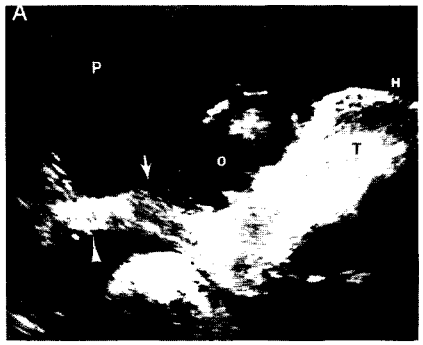

Fig. 2. Sonographic finding in acardiac twins, showing hydropic fetus without head, and also omphalocele.

4. Color Doppler velocimetry

Color Doppler may help to look in detail at fusion site of conjoined twins, for example, common liver arterial circulation or common cardiac systems. Its details can confirm diagnosis and suggest therapy after births.[21]

In acardiac twins, color Doppler may help to determine site of vascular connection, assess circulatory health of the normal fetus, and assess sign of heart failure or hydrops in the pump twin.[24,25]

In congenital malformations not unique to twins, color Doppler is helpful to assess fetal health status, and much helpful to confirm diagnosis in congenital heart defects.

5. Fetal echocardiography

Fetal echocardiography is exclusively helpful to establish diagnosis for congenital heart defects and plan the management.[27]

6. Chromosome study

Chromosome study is usually unneeded in conjoined twins, acardiac twins, and twins with neural tube defects. In twins with heart, GI, and KUB anomalies, chromosome study is usually required, it can be performed pre-natally by amniocentesis or cordocentesis.[28] When one anomaly has been detected, other anomalies must be looked for, and if there are multiple , chromosome study is required. [28] Some chromosome anomalies have more prevalence in twins than in singleton, such as 45,XO (Turner syndrome), 47,XXY (Klinefelter syndrome), therefore, when routine ultrasound scanning is performed, it must also be realized to look for detectable sonographic findings of those chromosome anomalies , for example, cystic hygroma, lymphangioedema, ascites, congenital heart disease, renal anomalies, and oligohydramnios can be observed in Turner syndrome, and if these findings are detected, chromosome study is required.[29]

7. Gross descriptions

Gross descriptions of the fetuses after birth or termination are definitive diagnosis for conjoined twins, acardiac twins, and twins with neural tube defects. For twins with congenital heart , GI, and KUB anomalies, further investigations including an autopsy may be required for definitive diagnosis.[5,9] Examples of grossly malformed neonates are shown in Figure 3 and 4.

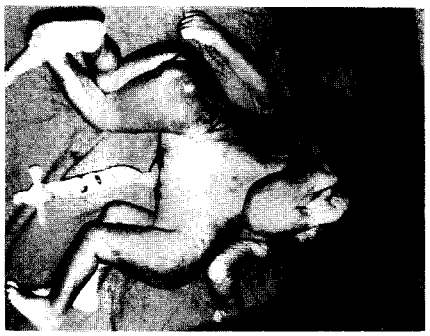

Fig. 3. Newborn with thoracopagus

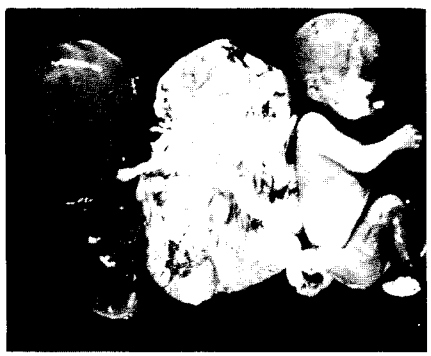

Fig. 4. Newborn with acardiac twins

Management

Antepartum, intrapartum, and postnatal management of conjoined twins and acardiac twins are discussed in Table 3.

anencephalic fetuses, the affected fetus is precisely not able to survive after birth. If twin pregnancy is concordant for anencephaly, management is simple by termination. But in

For congenital malformations not unique to multiple conception, management must be individually decised upon nature of disease, chorionicity of twins, compatibility to survive after birth, possibility of treatment, and prognosis. Decision must also follow parental discussion.[1,2] For example, in twins that have case of twins, which is much more common, discordant

Table 3. Management of conjoined twins and acardiac twins.[8,30-33]

	Antepartum	Intrapartum	Postnatal
Conjoined twins	1.Perform fetal echocardiography to assess cardiac structure, and serial ultrasound every 3-4 weeks to monitor growth and fetal demise. 2.Consult neonatologist and child surgeon to assess prognosis for separation and perinatal plan. 3.No fetal therapy is indicated, except releasing polyhydramnios.	1.Termination of pregnancy may be discussed with parents if early diagnosis is made 2.At delivery, well planned cesarean section in tertiary center is advised.	1.Respiratory support must be ready as early as first breath of life, as well as warmth, nutrition, and protection from infection. 2.Separation is varied on severity and timing must be discussed.
Acardiac twins	1.Serial ultrasound every 1-2 weeks to assess growth status, hydrops,or death of the pump twin. 2.Fetal therapy may be attempted, such as maternal digitalization, serial amniocentesis, maternal indomethacin therapy, endoscopic cord ligation, thrombosis of the umbilical artery by percutaneous thrombogenic coil or laser therapy, and hysterotomy with selective delivery of the perfused twin.	1.Conservation as long as possible until complications develop in the pump twin, then delivery is indi-cated, and should be performed in tertiary center. 2.Vaginal delivery is allowed unless fetal distress.	1.Respiratory support is essential, care must be emphasized on cardiac function as heart failure is commonly developed. 2.Prematurity is very common, care for RDS must be prepared. 3.Support parents for inevitable death of the perfused twin.

for anencephaly, chorionicity must be one of the determining factor. In monochorionic twins, expectant management is the only way unless the other fetus is unhealthy. In dichorionic twins, selective fetocide may be performed to prevent complications of twin pregnancy such as preterm labour, malpresentation, and iron deficiency anemia. It is also able to prevent polyhydramnios from anencephalic fetus that can superimpose complications of twin pregnancy, and can reduce cesarean section rate especially from twin associated indication but the parents can look after only one child. Amniocentesis to release polyhydramnios is another one of the management options. However, counseling with the parents is essential because each procedure has its risks. For example, selective fetocide in the second trimester-dichorionic twins proves to prevent the development of polyhydramnios and is associated with a lower risk of preterm delivery but can cause miscarriage upto the one-fifth of cases.[34] While there is some suggestion that expectant management may produce more favorable outcome for the unaffected fetus with no higher risk of miscarriage from a selective termination and has acceptable short and long term outcomes to the infants.[35] These options and risks must be discussed with the parents and treatment of other congenital malformations not unique to multiple conception should follow by this demonstration.

Prognosis

In conjoined twins, prognosis for survival depends on potential for separation of the connected infants which is related to the location of the union, the status of share vital organs, and the presence of associated organ malformations.[8] Well planned elective cesarean section in tertiary center also help to improve prognosis.[9] Timing for separation has effect on success rate and long term survival, the best result encounters when separation has been performed in the second and third month of life.[30]

In acardiac twins, all of the perfused twins die, while the pump twin has a 50 percent mortality rate.[9] The pump twins most commonly die from congestive heart failure, the rests are from prematurity.[36] It is found that the mean birthweight ratio in twins born before 34 weeks was up to 60 percent.[36] Well planned perinatal management in tertiary center by prenatally diagnostic ultrasound can help to improve prognosis.

In congenital malformations not unique to multiple conception other than positional defects, prognosis depends on severity of anomaly, associated anomalies, number of affected fetuses (concordant or discordant), and management policy.[4,5] For positional defects ; i.e. , talipes, skull asymmetry, and hip dislocation, all have excellent prognosis with mostly quick and spontaneous resolution and there is no recurrent risk.[5,6]

Discussion

Congenital malformations in twins are not uncommon. The malformations unique to multiple conception are special, obstetricians should have knowledge on them, especially to diagnose. Management should be obtained in tertiary center. In malformations not unique to multiple conception, it is exclusively striking to try to understand their hypotheses because their prevalent rates are increased in twins. As previously mentioned , there are explained by twinning process, vascular interchange, and so on. But finally, some investigators propose that may twins itself be a malformation process? More studies are needed.

Twins may be one of good models to study about congenital malformations and their clinical relevant. Examples, difference in FHR patterns between anencephalic and normal fetus were observed after week 28th in monozygotic twins with discordant anencephaly[37], and difference in fetal behavior observing in 2nd and 3rd trimester may indicate that the development of the CNS above the medulla oblongata plays an important role in fetal movement and fetal breathing movement.[38] Other instances, there are reports about malformations occurring from genetic disorder with same genotypic defects in twins which cleavage from the same zygote (monozygotic twins) but have different or variable phenotypic expression[39,40], it indicates that embryology is complicated with may sometimes not be able to be simply explained. Therefore, it is discussed that twins are one of good models for genetic and embryologic learning. Other studying and reports is really required.

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OBSTETRICS

Genetic Amniocentesis for Prenatal Diagnosis at Pramongkutklao Hospital: A six-year report

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ABSTRACT

Objective To evaluate results of amniocentesis for prenatal diagnosis of chromosome abnormality and analyze Down syndrome controlling program using maternal age cut-off at Pramongkutklao Hospital.

Method Records of mothers who had genetic amniocentesis during 1 October 1990-30 September 1996 were reviewed. Records of abnormal chromosome in newborns and numbers of mothers who delivered at Pramongkutklao Hospital at the same period were also studied.

Results During six years, 28,191 women, including 2,174 (7.71%) elderly gravida (>=35 years old), delivered at Pramongkutklao Hospital. 917 (3.25%) amniocentesis were done from 906 mothers (11 twin pregnancy) from the following indication: 1) elderly gravida 2) previous chromosome disorder 3) fetal malformation 4) familial history of chromosome disorder 14 (1.53%) major abnormal chromosomes were detected prenatally. 16 (1.74%) samples failed to culture. The indication that most commonly found major abnormal chromosome was fetal malformation (4/18), but no major abnormal chromosome was found from the Indication of previous chromosome abnormality and familial history of chromosome disorder. Most common major abnormal chromosome was Trisomy 21 (6/141). Our program to control incidence off Down syndrome using maternal age cut off at >=35 years old alone could access 782 (11 twin pregnancy) in 2,174 mothers (35.9%) and detect 5 Down syndrome fetus (5/793=1/159) and 3 other major abnormal chromosome fetus (8/793=1/99). Incidence of Down syndrome fetus and major abnormal chromosome born during this period were 0.89 and 1.56 /1,000 live births respectively. The program could detect 5/30 (16.6%) of Down syndrome fetus and 8/52(15.4%) of all major abnormal chromosome fetus.

Conclusion Elderly mothers were increasing. Although there was an increasing access to elderly mothers of the controlling program, the incidence of Down syndrome in our hospital did increase. Genetic counsellors, new methods of screening and confirmatory test as well as improvement of cytogenetic lab will be required in the near future.

Key words: prenatal diagnosis, amniocentesis, Down syndrome

Amniocentesis was first performed for genetic studies in the 1950. At the beginning, It used only for antenatal sex determination.[1] In 1966, prenatal diagnosis had begun, when Steele and Breg[2] cultured amniotic cells and analyzed their karyotypes. Subsequently, amniocentesis has been performed for the diagnosis of variety disorders including chromosomal abnormality. In developed countries, it has been offered to women with an increased risk of having a child with chromosome abnormality, neural tube defect or metabolic disease.

Pramongkutklao Hospital has established the program of genetic counseling and prenatal diagnosis with midtrimester amniocentesis since 1985. The program was aimed to control the incidence of chromosome abnormality especially Down syndrome in live birth. Results of the first six years were studied by Ketupanya.[3] After that, the numbers of genetic amniocentesis has been increasing year by year, along with the numbers of elderly gravida. The purpose of this study is to evaluate the results of genetic amniocentesis in the following six years and analyzes Down syndrome controlling program using maternal age alone at Pramongkutklao hospital.

Method

Records of women who had genetic amniocentesis during 1 October 1990-30 September 1996 were reviewed. Records of abnormal chromosome neonates and women who delivered at Pramongkutklao hospital during the same period were studied.

Program of genetic counseling and prenatal diagnosis at Pramongkutklao Hospital

Elderly gravida (>=35 years old) who came to antenatal clinic during 16-20 gestational weeks were appointed to genetic clinic. After process of counseling and signing consent form, physicians performed ultrasonographic study to screen fetal anomaly and confirm dating. Amniocentesis was done and 30 cc of amniotic fluid was aspirated. After the procedure, ultrasound examination was repeated to confirm fetal heart motion. Amniocytes were cultured in three different flasks. After harvesting and spreading the chromosome on the slides, we used Trypsin and Geimsa staining technique for banding. The chromosome were analyzed for 15-25 metaphases, photographed and karyotyped for 2 mataphases.

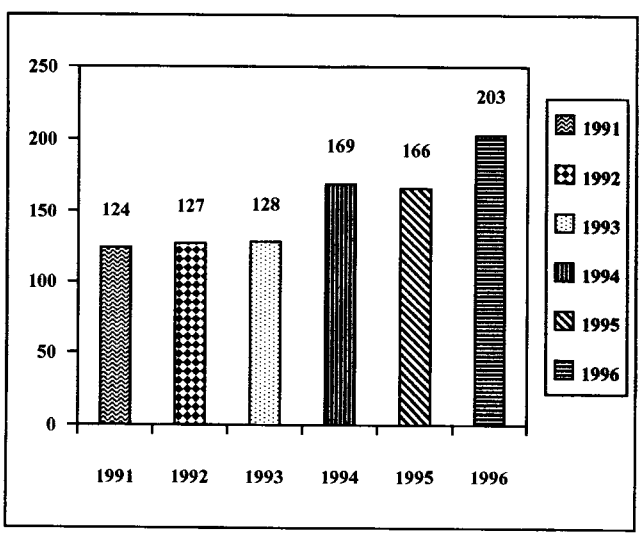

Fig. 1. Total numbers of amniocentesis by years.

Table 1. Numbers and results of amniocentesis by years

YEARS	NUMBERS	RESULTS								
		NORMAL	FAIL	%	UNKNOWN	%	MAJ. ABN.	%	OTHER ABN	%
1991	124	107	3	2.42	10	8.06	0	0.00	4	3.23
1992	127	123	0	0.00	3	2.36	1	0.79	0	0.00
1993	128	123	0	0.00	3	2.34	2	1.56	0	0.00
1994	169	160	0	0.00	3	1.78	4	2.37	2	1.18
1995	166	147	9	5.42	3	1.81	4	2.41	3	1.81
1996	203	194	4	1.97	1	0.49	3	1.48	1	0.49
TOTAL	**917**	**854**	**16**	**1.74**	**23**	**2.51**	**14**	**1.53**	**10**	**1.09**

Table 2. Results of amniocentesis by age distribution

AGES	TOTAL No. OF DELIVERY	RESULTS									
		No. of Amnio	Maj. Abn.		Other Abn.		NORMAL		FAIL		UNKNOWN	
<20	3,175	5	0	0.00	1	20.00	4	80.00	0	0.00	0	0.00
20-24	8,542	13	0	0.00	0	0.00	10	76.92	1	7.69	2	15.38
25-29	9,056	52	2	3.85	1	1.92	46	88.46	0	0.00	3	5.77
30-34	5,244	51	4	7.84	2	3.92	43	84.31	1	1.96	1	1.96
35-39		640	5	0.78	6	0.94	604	94.38	13	2.03	12	1.88
40-44	2,174	152	3	1.97	0	0.00	144	94.74	1	0.66	4	2.63
>44		2	0	0.00	0	0.00	2	100.00	0	0.00	0	0.00
UNKNOWN		2	0	0.00	0	0.00	1	50.00	0	0.00	1	50.00
TOTAL	**28,191**	**917**	**14**	**1.53**	**10**	**1.09**	**854**	**93.13**	**16**	**1.74**	**23**	**2.51**

Table 3. Results of amniocentesis by indications

INDICATIONS	NUMBERS OF AMNIO.	RESULTS									
		NORMAL		MAJ. ABN.		OTHER ABN.		FAIL		UNKNOWN	
1. AGE 35-37	427	406	95.08	4	0.94	3	0.70	7	1.64	7	1.64
2. AGE >=38	366	343	93.72	4	1.09	3	0.82	7	1.91	9	2.46
3. PREV. CHRO. ABN.	28	26	92.86	0	0.00	2	7.14	0	0.00	0	0.00
4. MALFORMATION	18	13	72.22	4	22.22	0	0.00	1	5.56	0	0.00
5. FAMILIAL HX	8	7	87.50	0	0.00	1	12.50	0	0.00	0	0.00
6. OTHER	55	52	94.55	2	3.64	1	1.82	0	0.00	0	0.00
7. UNKNOWN	15	7	46.67	0	0.00	0	0.00	1	6.67	7	46.67
TOTAL	**917**	**854**	**93.13**	**14**	**1.53**	**10**	**1.09**	**16**	**1.74**	**23**	**2.51**

Table 4. Major chromosome abnormalities

TYPES OF ABNORMALITY	NUMBERS
47, XX,+21	5
47, XY,+21	1
47, XY,+18	2
47, XX,+13	1
46, XX,t(13q 14q)	1
45, XO	1
45, XO/46, XX	1
46, X, i(Xq)/45, XO	1
47, XXY	1
TOTAL	**14**

Table 5. Other chromosome abnormalities

BALANCED TRANSLOCATION and INVERSION	
1. TYPES OF ABNORMALITY	NUMBERS
46, XX t(2, 18) BL translocation	1
45, XY t(13q14q) BL translocation	1
Total	**2**
2. MARKER CHROMOSOME	
46, XX, INV (2)(p13, q11)	1
47, XX, ISO 15p	1
Total	**2**
3. NORMAL VARIATION	
46, XX, 21 P+	1
46, XX, 15 P+	3
46, XX, 16 qh+	1
46, XX, 16 qh+	1
	6
TOTAL	**10**

Table 6. Abnormal chromosomes distributed by ages and indications

NO.	TYPES OF ABNORMAL	MATERNAL AGES	INDICATIONS
	MAJOR ABNORMAL CHROMOSOMES		
1	47, XX, +21	36	AGE 35-37
2	47, XX, +21	34	ANXIETY
3	47, XX, +21	37	AGE 35-37
4	47, XX, +21	37	AGE 35-37
5	47, XX, +21	42	AGE >=38
6	47, XY, +21	42	AGE >=38
7	47, XY, +18	39	AGE >=38
8	47, XY, +18	26	DIL.CISTERNA MAGNA, CLENCH HAND
9	47, XX, +13	32	HOLOPROSENCAPHALY
10	46, XX,-14,+t (13q14q)	26	HOLOPROSENCAPHALY
11	45, XO	34	CYSTIC HYGROMA
12	45, XO / 46, XX	37	AGE 35-37
13	46, X, i (Xq) / 45, XO	34	ANXIETY
14	47, XXY	43	AGE >=38
	OTHER ABNORMAL CHROMOSOMES		
15	46, XX t (2,18) BL translocation	26	TRANSLOCATION MOTHER
16	45, XY, t (13q, 14q) BL translocation	30	TRANSLOCATION FATHER
17	46, XX, inv (2)(p13 q11)	31	AGE 35-37
18	47, XX, iso 15p	38	AGE >=38
19	46, XX, 21 p+	30	PREVIOUS ANENCEPHALY AND ANXIETY
20	46, XY, 15p+	39	AGE >=38
21	46, XY, 15p+	39	AGE >=38
22	46, XY, 15p+	37	AGE 35-37
23	46, XX, 16qh+	36	AGE 35-37
24	46, XX, 16qh+	19	PREVIOUS CHROMOSOME ANOMALY

Table 7. Analysis of Down's syndrome controlling program using maternal ages alone

YEARS	1990	1991	1992	1993	1994	1995	TOTAL
NO. OF MOTHERS DEL. AT PMK HOSP.	4374	4692	4742	4723	5020	4640	28191
MATERNAL AGE >=35	289	359	369	364	370	423	2174
RATIO TO ALL DEL.	6.61%	7.65%	7.78%	7.71%	7.37%	9.12%18	7.71%
NO. AMNIO. BY AGE INDICATION ALONE	100	110	109	144	147	3	793
RATIO TO ALL ELDERLY GRAVIDA	34.60%	30.64%	29.54%	39.56%	39.73%	43.26%	36.48%
NO. DOWN DETECTED FROM AMNIO.*	0	0	1(1/109)	0	3(1/49)	1(1/183)	5(1/159)
NO. OF ALL MAJ. ABN. CHRO. FROM AMNIO.*	0	0	1(1/109)	2(1/72)	3(1/49)	2(1/91)	8(1/99)
LIVE BIRTHS	4387	4696	4689	4723	5034	4648	28177
NO. OF DOWN AT BIRTH	5	0	6	6	1	7	25
DOWN INCIDENCE (/1000 LB)	1.14	0.00	1.28	1.27	0.20	1.51	0.89
NO. OF MAJ. ABN. CHRO. AT BIRTH	8	4	9	9	5	9	44
INCIDENCE OF MAJ. ABN. CHRO. (/1000 LB)	1.82	0.85	1.92	1.91	0.99	1.94	1.56

* = BY AGE INDICATION ALONE

Total 8. Abnormal chromosomes found at birth with no prenatal diagnosis

	MATERNAL AGES				
	<35	35-37	>=38	UNKNOWN	TOTAL
DOWN SYNDROME	8	5	3	9	25
OTHER ABNORMAL CHROMOSOMES	11	3	5	0	19
TOTAL	19	8	8	9	44

Result

During the study period, The numbers of amniocentesis were increasing from 124 in 1991 to 203 in 1996 (Fig. 1). Total of 917 (3.25%) samples of amniotic fluid were drawn from 906 mothers 11 twins pregnancy). There were 24 abnormal chromosome, 14 (1.53%) were major abnormal chromosome, 10 (1.09%) were minor abnormal chromosome. 16(1.74%) samples were failed to culture. The results of 23 (2.51%) samples were missing (Table 1). During the same period, there were 28, 191 women who delivered at Pramongkutklao hospital. 2,174 (7.18%) were elderly gravida (>= 35 years old). Age of patients who had amniocentesis ranged from 17-45 (mean 36.3± 4.34). Out of 917 amniocentesis, 794 samples were done from 782 (35.9% of 2,174) elderly mothers (11 twins pregnancy) from the indication of age alone and another 1 elderly mother from the indication of malformed fetus. We could detect 8 major abnormal chromosome fetus prenatally from the elderly group and other 6 major abnormal chromosome fetus from the younger age group (Table 2). Indication for chromosome study were listed in Table 3. The most common indication that resulted in major abnormal chromosome was fetal malformation (4 in 18), but no major abnormal chromosome was found from the cases of previous chromosome abnormality and familial history of chromosome disorder. The numbers of, amniocentesis performed from indication of maternal aged 35-37 and aged >=38 were 427 and 366 respectively. Most common major abnormal chromosome was 21(6 in 14), the other were Trisomy 18, Trisomy 13, monosomy X, mosaic monosomy X and 47 XXY. (Table 4) The other minor abnormality were 3 balanced translocation and inversion, 1 marker chromosomes and 6 normal variations (Table 5). 5 Trisomy 21 and 3 other major abnormal chromosome were detected prenatally by aged indication alone (Table6). From this study, program to detect Down syndrome fetus using maternal age cut off at >= 35 years old, could access only 782 in 2,174 mothers (35.97%) and could detect 5 Down syndrome fetus (5 in 793 = 1/159) or 8 major abnormal chromosome fetus (8 in 793 = 1/99) from 793 samples. Incidence of Down syndrome and major abnormal chromosome fetus at birth during that period were 0.89 and 1.56/1000 live birth respectively. Therefore the program could detect only 5 in 30 (16.6%) of Down syndrome fetus and 8 in 52 (15.4%) of all major abnormal chromosome fetus prenatally (Table 7). When we analyzed 44 major abnormal chromosome fetuses born during the same period, there were 25 Down syndrome fetus and 19 major abnormal chromosome fetus. In the Down syndrome group, 8 were from mothers younger than 35 years old, 5 from mothers aged 35-37, 3 from mothers aged >= 38 and 9 from mothers whose age couldn't be identified. In the other major abnormal chromosome group, there were 11, 3, 5, 0 from the corresponding maternal age respectively. (Table 8)

Discussion

Program of genetic counseling and amniocentesis in Pramongkutklao hospital has been established since 1985. The result of the program during 1985 to 1990 was presented by Ketupanya.[3] Since then, the numbers of genetic amniocentesis has been increasing every year from 124 in 1991 to 203 in 1996 (Table 1).

14 (1.53%) major abnormal chromosome from 917 samples were detacted prenatally. 10 (1.09%) other abnormal chromosome in this study refer to marker chromosome, balanced translocation, inversion and normal variation which have no significant clinical features. Overall fail cultured rate, was 1.74% which was the same as other studies (1-2%).[4] In 1995, 5% failed culture rate was from the problem of fungal infection in ventilatory system around cytogenetic laboratory room.

During six years, 28191 mothers, including 2174 (7.71%) elderly mothers, delivered at Pramongkutklao Hospital. We could perform 793 amniocentesis from 782 mothers (35.9%) when we used aged indication alone which was higher than access rate of Suwajanakorn's study in 1991-1992 (20.8%).[5] The reasons why we could not perform amniocentesis In all elderly mothers were late antenatal care, physician's negligence or patient's avoidance, which should be another issues to study further to increase the amniocentesis rate in our hospital.

Indication most commonly found abnormal chromosome was fetal malformation (4/18), but no abnormal chromosome was found from the indication of previous chromosome abnormality and familial history of chromosome disorder. This may be the result of small sample size (26 cases). Other indication in this study refered to previous neural tube defect, maternal anxiety and IVF pregnancies.

Most common major abnormal chromosome detected prenatally was Trisomy 21 (6/14), which was the same as other studies. The others were Trisomy 18, Trisomy 13, monosomy X, mosaic monosomy X and 47 XXY.

From the result catergorized by indication, when we used the maternal aged out off at >= 35 years old, we could detect 5 Down syndrome fetus (5 in 793 ~ 1/159) and 3 other major abnormal chromosome fetus (8 in 793 ~ 1/99) when performed 793 amniocentesis (table 3,6) Compared to the rate of 1/140 from other studies,[6] our program had a slightly lower rate of detecting Dawn syndrome fetus. If we used the cut off at >=38 years old, we could detect 2 Down syndrome fetus (2 in 366 = 1/1183) and 2 other major abnormal chromosomes for total detection rate of 1/90 (4 in 366) (table 3,6). The changing of the cut off age from 35 to 38 years old was debated during the last few years in our hospital. The cost effectiveness of both cut-offs had been estimated from the provider's view point in Ketupanya's study. They were 67,129 VS 36,617.7 Baht / case detection respectively.[3] However, from the parent's view point, we will miss 3 fetus of Down syndrome and another 1 abnormal chromosome fetus. This problem will burden their family and society eventually. This subject of debate came from the increasing numbers of elderly mothers and work load on cytogenetic lab.

With increasing numbers of elderly mothers who came to deliver at Pramongkutklao Hospital from 4,374 in 1991 to 5,020 in 1995 and the increasing proportion of elderly mothers from 6.61% in 1991 to 9. 12% in 1996, even we could increase access to elderly mothers from 34% in 1991 to 43% in 1996, the incidence of Down syndrome at birth did increase to 1.51/1000 live birth in 1996. (Table 6) When analyzed abnormal chromosome fetus born at the same period. if we had performed amniocentesis to all elderly mothers we could have detected other 8 Down syndrome and 8 other major abnormal chromosome fetus prenatally, but we still missed more than 8 Down syndrome and 11 other major abnormal chromosome fetus (Table 8). Therefore, new methods of screening and confirmatory test, increasing rate of access to elderly mothers, genetic counsellors as well as improvement of cytogenetic lab will be required in the near future in our hospital.

New markers to screen Down syndrome fetus especially the triple markers have been established in 1992.[7,8] Some suggest to use them to screen only mothers younger than 35 years old or to be another option for older women, who traditionally have all been considered candidates for amniocentesis. We will not incorporate them into our program until we can make sure that we can provide adequate pretest genetic counseling and our lab can manage with the increasing numbers of serum markers to be tested as well as

cytogenetic samples. Importantly, the cost effectiveness of the program in our population should be considered carefully.

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OBSTETRICS

Prediction of time to delivery: Elective induction versus Spontaneous Labor

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ABSTRACT

Objective To predict time to delivery after in labor between elective induction and spontaneous labor.

Study design Retrospective cohort study.

Setting Ramathibodi Hospital, a 800-beds medical school hospital in Bangkok.

Study Population All patients who visited at antenatal care clinic and delivered at Ramathibodi Hospital, Bangkok, during the calendar year 1997.

Subjects The study factor was the mode of in labor, elective induction and spontaneity. Two-hundred and thirty patients for each group were randomly selected from the registration. All patients were single fetus, gestational aged 37 to 41 weeks, regular menstrual cycle with accurate last menstrual period, and cephalic presentation. We excluded patients who had previous or current obstetric/medical complications.

Main outcome The outcome variable was the time elapsed between labor onset and delivery. Vaginal delivery resulted in a completed time and cesarean section was the censoring event.

Analysis Kaplan-Meier was applied to determine the probability of vaginal delivery after labor was initiated. Cox hazard model was used to estimate the risk of vaginal delivery after adjusting for confounding variables.

Result There were 381 patients who delivered via vagina and 50%of patients delivered at 7.3 hours after in labor. The medians of vaginal delivery time were about 6 hours and 9 hours for induce and spontaneous group. For induce group, the probability of vaginal delivery at 4, 8, and 12 hours after initiating labor were 26.1% (95% CI 20.9% - 32.2%), 71.8% (95% CI 65.3% - 77.9%), and 90.1% (95% CI 83.5% – 94.9%). These were much higher than finding in spontaneous group, the corresponding probability were 7.8% (95% CI 5.0% - 12.1%), 41.6% (95% CI 35.6% - 48.3%), and 53.4% (95% CI 47.1% - 60.1%) respectively. After adjusting for confounding variables, elective induction was more likely to have vaginal delivery than in spontaneous group (HR = 2.4, 95% CI 1.8 –3.1).

Conclusion When compared to spontaneous labor, elective induction appears to have much shorter time to delivery.

Key words: prediction, time to delivery, elective induction, spontaneous labor

Elective induction of labour is defined as an initiation of labour, either by mechanical or pharmacologic means, at a time earlier than nature with regardless to a medical or obstetric indication.[1-4] Some authors are not enthusiastic in elective induction since they think that unnecessary elective induction increases the risk in maternal and fetal morbidity.[4] The morbidity event that should be mostly avoided in neonates is prematurity which results in pulmonary immaturity.[4-5] However, the ability to assess fetal and maternal risks has recently increased, as has obstetricians understanding of the mechanism of labour. As a result of this, elective induction is more likely to end in a successful and safe outcome.

Ideally, labor should be allowed to occur spontaneously. Currently, most patients and also obstetricians prefer elective induction rather than spontaneous labour. Patients give reasons such as a greater knowledge of the exact date of birth, which allows them to make arrangements regarding their work commitments, care of other children during hospitalization, family members, and also leads to more peace of mind. From an obstetrician's point of view, they prefer to set the delivery time during the daytime of workday when related teams such as obstetrician staff, anesthetists, pediatricians, and nursing teams are more likely to be available, rather than at after hours or during the weekend.

After in labor, time to delivery is an interested outcome for patients and also obstetricians. Some studies had estimated and compared the length of labor between two modes of labor (MOL),[2-3, 6-8] elective induction and spontaneous labor, but did not estimate the probability of delivery in hourly with this regard. Bremme et al[9] conducted study to predicted time to delivery only one group of labor, induction. We, therefore, conducted a retrospective cohort study in order to predict time to delivery in hourly between elective induction and spontaneous labor.

Methods

A retrospective cohort study was conducted which included women who had visited an antenatal care clinic and delivered at Ramathibodi Hospital, Bangkok, Thailand, between January 1 to December 31 1997. Ramathibodi Hospital is a governmental tertiary hospital and medical school. There were 5879 deliveries during the study time period, of which 1400 (23.8%) births were induced and 4495 (76.2%) were spontaneous. Women were eligible for the study if they had a single fetus with a gestational age of between 37 to 41 weeks and cephalic presentation, and had a regular menstrual cycle with accurate LMP. Also excluded were all patients who had previous or current obstetric/medical complications, or were induced because of medical indication.

The focus of this study was mode of labor (MOL), either elective induction or spontaneous labor. Prior sample size calculations indicated a random sample of 230 women from each group. These were selected randomly by computer generation of random numbers. The method of induction consisted of amniotomy following about one to three hours after Oxytocin infusion, or intravenous Oxytocin infusion followed by amniotomy, or prostaglandin E2 gel suppositories, or any combination thereof. Oxytocin dosage was 5 units, diluted in 5% dextrose in 1000 ml of water. The start rate was 10 drops per minute and this could be increased through 20 and 40 to a maximum of 60 drops per minute every 30 minutes until the intensity of uterine contraction was moderate and with duration of about 30 seconds. For the control group, spontaneous labor was defined as the onset of pain and regular uterine contraction every 10 minutes or less, with or without mucous bloody show or rupture of membranes. During their stay in a delivery room, these women may have received stimulation by intravenous Oxytocin infusion. The protocol of Oxytocin infusion was the same as that for the induced group.

The outcomes of interest were time to vaginal delivery (normal labor, vacuum extraction, and forceps extraction). Time to vaginal delivery was calculated from time at the onset of labor to time at vaginal delivery. Time at the start of Oxytocin treatment, amniotomy, or PGE2 suppositories, was defined as time at the onset of labor for the induced group. For the spontaneous

group, patients were asked by nurses to recall what time they felt regular pain before they came to hospital. Nurses also observed uterine contraction for an hour after admission. If the frequency of contraction was 10 minutes or less and patients could recall an accurate commencement time, we used this time to mark the onset of labor. Otherwise, we used the time of the first observed uterine contraction with an interval of less than 10 minutes from the previous contraction. In Ramathibodi Hospital, the chief residents of obstetrics (or staff for private cases) are responsible for the decisions relating to obstetric deliveries, including choice of delivery mode. The indications for each were clearly defined and all involved obstetricians were asked to observe strict compliance. In practice, well-trained nurse specialists would observe uterine contraction and fetal heart rate every 15 minutes while the women were receiving Oxytocin, or every 30 minutes in the case of aminiotomy only.

A senior nurse specialist (the second author) reviewed women's records. Data collected included time of onset labor, time of delivery, mode of delivery, parity, age, weight at first visit, weight at delivery, maternal height, use of analgesics, type of case (service/private), evidence of intra-postpartum complication, Apgar score, cervical examination, and birth weight. If there was any problem in the data recording, especially in time of labor onset, consensus was reached with assistance from a senior obstetrician. Confounding variables which had been recorded, such as age, maternal height, weight gain during pregnancy, type of case, parity, gravida, gestational age at delivery, and cervical status at onset of labor were considered and included in analysis. The only available information on cervical status was cervical dilation, cervical effacement, and station. Thus a modified Bishop score[8] was used as a surrogate variable to measure cervical ripening.

The software package EPI INFO was used for data base management. A data-checking file was developed in order to control the quality during data entry. After the data were checked, analyses were conducted using STATA (version 5.0).[10] Depending on the outcome and distribution of data, t-tests, Mann-Whitney tests, and Chi-squared tests, were used to compare various characteristics between two groups. Kaplain-Meier method was applied to estimate probability of vaginal delivery in hourly after labor was initiated. Cesarean section was claimed to be censored in analysis. Log rank test was applied to compare the probability of vaginal delivery between two MOL. Cox hazard model was used to determine the risk of vaginal delivery among MOL after adjusting for confounding variables.

Results

Patients' Characteristics

All 230 women in each group were included in the analyses. General characteristics of patients are shown below (Table 1). There was no difference between groups for maternal ages, height, education level, gravida, and weight gain during pregnancy. There were significant differences in gestational age at delivery, parity, Bishop score, and type of case between the two groups. Gestational age at delivery ranged between 37 to 41 weeks for both groups. The proportion of nulliparous pregnancies in the induced group was 53.48% and, in the spontaneous group, 64.35%. The mean of Bishop score at the onset of labor was 4.12 (1.52) for the induced group and 4.64 (1.59) for the spontaneous group. Most women in the induced group (68.26%) were private cases, while only 37.83% were private cases in the spontaneous group.

Time to Delivery

There were 381 (82.83%) of patients who delivered via vagina. 50% of patients delivered at 7.3 hours after in labor. The outcome of interest was the time elapsed between labor onset and delivery. Vaginal deliveries resulted in a complete time and cesarean section was the censoring event. A Kaplan-Meier curve was used to estimate the probability of delivery after in labor. We found that, after labor was initiated in, delivery time for the induced group was much shorter than for the spontaneous group (Figure 1). The median time for the induced group was about 6 hours while it was 9

hours for the spontaneous group. For the induced group, the probability of deliveries within 4, 8, and 12 hours were 26.1%, 71.8% and 90.1% respectively, with the corresponding estimated 95% confidence intervals were 20.9%-32.3%, 65.3%-77.9% and 83.5%-94.9%. Compared to the spontaneous group, the corresponding probability were much lower; 7.8% (95% CI = 5.0-12.1), 41.6 (95% CI = 35.6-48.3) and 53.4% (95% CI = 47.1-60.1) respectively. A log rank test to compare the two MOL groups was highly statistically significant ($p < 0.0001$).

Table 1. Comparison of Characteristics between Elective Induction and Spontaneous Groups

Characteristics	MOL Groups		P-value
	Induction (n=230)	Spontaneous (n=230)	
Education level; number(%)			
6 yrs	43(18.7)	47(20.4)	.456*
6-12 yrs	82(35.7)	92(40.0)	
13-14 yrs	24 (10.4)	16 (7.0)	
15 yrs	81(35.2)	75 (32.6)	
Age in year mean (SD)	29.4 (4.8)	28.6 (4.7)	.066**
Maternal Height (cm) mean (SD)	156.0 (5.3)	156.2 (5.2)	.646**
Weight Gain (kg) median (range)	13.5 (5.0-22.5)	13.6 (4.9-26.0)	.594***
Gestation Age (week) mean (SD)	39.2 (0.1)	38.6 (0.1)	<.001**
Bishop Score mean (SD)	4.1(1.5)	4.6 (1.6)	<.001**
Gravida; number (%)			
1	93 (40.4)	113 (49.1)	.061*
2	88 (38.3)	84 (36.5)	
3	43 (18.7)	22 (9.6)	
4	6 (2.6)	11 (4.8)	
Parity; number (%)			
0	123 (53.48)	148 (64.35)	.043*
1	85 (36.96)	69 (30.00)	
2	22 (9.57)	13 (5.65)	
Type of cases; number (%)			
Private	157 (68.26)	87 (37.83)	<.001*
Service	73 (31.74)	143 (62.17)	

* Chi-square test, ** t-test, *** Mann-Whitney test

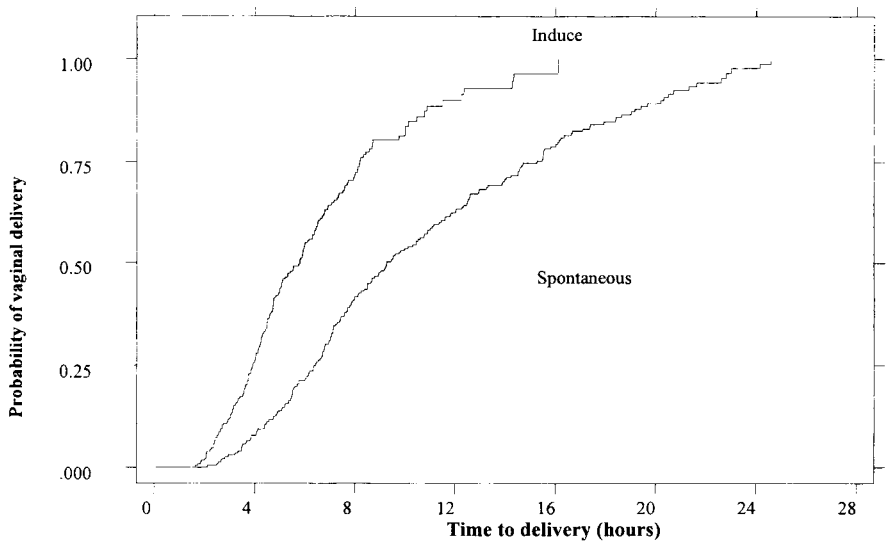

Fig. 1. Estimation of time to delivery between elective induction and spontaneous labor.

Cox's proportional hazards model was used to determine the probability of vaginal delivery after adjusting for some confounding variables such as age, type of cases, gestational age at delivery, weight gain during pregnancy, maternal height, education level, parity, Bishop's score, and gravida. We found that MOL, parity, Bishop's score, and the interaction between MOL and parity were significant (Table 2). The assumption that the hazard of vaginal delivery was constant for each different combination of variables was checked and verified. After adjusting for Bishop's score, nulliparous patients whose labor were elective induced were 2.4 times (95% CI =1.8 –3.1) more likely to have a vaginal delivery compared to nulliparous patients in spontaneous group. The probability of vaginal delivery increased dramatically if there was non-zero parity. For instance, induced women who had previously delivered 1, 2, or 3 times would have a chance of vaginal delivery 4.0, (95% CI = 3.1-5.3), 6.8 (95% CI = 4.1-11.3), and 11.5 (95% CI = 5.2-25.7) times higher than those with a spontaneous delivery. Bishop's score also affected the vaginal delivery rate; for each unit increased, the chance of vaginal delivery increased 1.4 times (95% CI = 1.3-1.5). This means that patients who had a Bishop's score of 5 at the onset of labor would have a chance of vaginal delivery which was 4.7 (95% CI = 3.3-6.7) times higher compared with patients whose Bishop's score was 0.

Table 2. Harzard Rates, 95% Confidence Interval for the Mode of in Labor and Confounding variables in Cox Model

Factors	Adjusted HR	95% CI for HR
Mode of in labor		
Induce	2.36	1.78 - 3.14
Spontaneous	1	
Parity	1.55	1.23 - 1.94
Bishop score	1.36	1.27 - 1.46
MOL x Parity	1.69	1.24 - 2.31

Discussion

In this study ,the elective induced group had much shorter time to delivery and resulted in higher probability of delivery at 4, 8, and 12 hours after in labor when compared to spontaneous group. Fifty percent of induced patients delivered at about 6 hours after labor while about 9 hours for spontaneous group. Increasing parity and Bishop score were very important factors in increasing the risk for vaginal delivery.

Three observational studies by Vierhout et al,[2] Macer et al,[3] and Yudkin et al[7] found that the length of labor was significantly shorter under elective induction than in spontaneous labor, while one observational, study by Cole et al,[11] found the time to be about the same. The length of labor is affected by many factors, which were not included in the analysis of these studies. On the other hand, reports on two randomized controlled trials gave conflicting results. Martin et al.[6] reported that the elective induction group had a longer labor time than a spontaneous group. This contrasts with a report by Tylleskar T, et al,[8] which found no difference in labor time between the two groups. A most important factor in determining this time is the accuracy of estimation of the time of onset of labor, especially in the spontaneous group. If the onset of labor is systematically under- or over-estimated, measurement of length of labor will be biased. Vierhout et al[2] had defined the onset of labor in a spontaneous group as the regular pain with an interval 4-5 minutes or as the moment of spontaneous rupture of membrane. However, some patients whose membranes ruptured spontaneously might not have regular pain and might take a long time to be in labor. This definition would may result in a long measurement of length of labor. Macer et al[3] defined length of labor in the same as Vierhout et al[2] but, with or without spontaneous rupture of membrane. However, neither study mentioned how they could verify the time of onset of regular pain. Martin et al,[6] Yudkin et al,[7] and Tylleskar T, et al[8] did not specify this definition. In our study, as much as possible was taken to estimate this from the medical record. In practice, patients in the spontaneous labor group go to the hospital when they have some sign or symptoms, which may result in true or false labor. Nursing specialists interviewed the women upon arrival and recorded when this sign or symptom had occurred and uterine contractions were observed during the first hour after admission. This information was then used to pinpoint the time of labor onset. However, since ours was a retrospective cohort study, all information was necessarily based on the available medical records.

In summary, when compared to spontaneous labor, elective induction appear to have much shorter time and higher probability of delivery.

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GYNAECOLOGY

Endometriosis in Infertile Women at Ramathibodi Hospital

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ABSTRACT

Objective To study the clinical characteristics of infertile women with endometriosis.

Design Retrospective descriptive

Setting Infertility clinic , Department of Obstetrics and Gynaecology, Faculty of Medicine, Ramathibodi Hospital

Subjects From 1993 to 1997, 56 infertile women were diagnosed with endometriosis, 45 cases (80.36%) by laparoscopy and 11 cases (19.64%) by laparotomy. The indications for diagnostic procedures were clinically suspected endometriosis and unexplained infertility.

Results The majority of infertile women with endometriosis were nulliparous (60.71%). The mean age at initial diagnosis was 32.55 + 3.99 years. Forty-eight women (85.71%) had dysmenorrhea mostly in a mild form (41.07%), and twenty women (35.71%) had dyspareunia. According to the stage of endometriosis, 19 cases (33.93%) were minimal, 22 cases (39.29%) were mild, and 15 cases (26.78%) were moderate to severe. The common sites for endometriotic lesion were the ovaries (57.14%) followed by the tubes (53.57%).

Conclusion The majority of infertile women with endometriosis were nulliparous with dysmenorrhea and dyspareunia. The endometriotic lesions at the ovaries and tubes were usually minimal and mild. Laparoscopy should be used to evaluate the clinically suspected endometriosis and unexplained infertility in the infertile women.

Key words : endometriosis, infertility

Endometriosis is an enigmatic disease, which at present can only be diagnosed through surgical mean either by laparoscopy or laparotomy. The symptoms of endometriosis, although characteristics, are extremely variable and not related to the stage of the disease.[1] The association between the occurrence of endometriosis and infertility has long been recognized. The etiology of infertility in endometriosis has been extensively researched. This relationship is obvious in women with severe endometriosis as the resultant of structural damage; ovarian and tubal adhesions prevent oocyte release, retrieval and transport leading to a mechanical disruption infertility. But in women with mild endometriosis and no apparent structural

damage the etiological basis for the infertility is unclear. Numerous factors have been investigated to explain how mild endometriosis could affect fertility. These factors include defective folliculogenesis, anovulation, hyperprolactinemia, luteinized unruptured follicle syndrome and luteal phase defects.[2,3] Other factors thought to lead to infertility in mild endometriosis include an autoimmune response resulting in implantation failure, alterations in the peritoneal fluid with inflammatory changes and an increased spontaneous abortion rate.[4-6] There are many studies evaluated the incidence of endometriosis, demographic and epidemiology, risk factors for the development of the disease, constitutional factors and menstrual characteristics associated with the disease, as well as familial and genetic factors.[7-10]

The objective of our study was to evaluate the clinical characteristics of infertile women with surgical diagnosis of endometriosis in the infertility clinic. For this purpose, we analyzed medical and infertility records of infertile women at the infertility clinic in Ramathibodi Hospital.

Materials and Methods

From 1993 to 1997, infertile women attending the infertility clinic of the Department of Obstetrics and Gynaecology, Ramathibodi Hospital for evaluation of infertility were included in the study. All of the women had a history of infertility more than 1 year and prospectively were subjected to our standard infertility evaluation, which included standard interview, physical and pelvic examinations, basic laboratory examinations, endometrial biopsy, CO_2 insufflation or hysterosalpingography and pelvic sonography before invasive investigation. Fifty-six infertile women who proceeded to diagnostic laparoscopy or laparotomy with clinically suspected endometriosis or unexplained infertility were diagnosed endometriosis. Their medical, menstrual and reproductive histories, as well as demographic and epidemiologic data were collected from medical and infertility records. Dysmenorrhea was recorded as none, mild, moderate, or severe. Mild, if there was minimal interferance with normal activities and usually no medication was required; moderate, if there was noticeable interference and mild analgesics were usually required; severe, if the women were unable to function normally and required strong analgesia and bed rest. Dyspareunia was recorded as present or absent. Stage of endometriosis and site of endometriotic lesions at the time of initial diagnosis were available on these women based on the review of operative reports according to the revised American Society for Reproductive Medicine classification.[11] Modes and results of treatment in each stage of endometriosis, including pregnancy outcome were recorded.

Results

From 67 cases of clinically suspected endometriosis and unexplained infertility, fifty-six women were diagnosed endometriosis, 45 cases (80.36%) by laparoscopy, and 11 cases (19.64%) by laparotomy. Thirty-four cases (60.71%) had primary infertility and 22 (39.29%) were pregnant previously. Eight of the twenty-two (36.36%) had spontaneous abortions, 8 (36.36%) had term pregnancies and 6 (27.28%) had induced abortions. The demographic data, menstrual characteristics, and infertility time are demonstrated in Table 1. Among the infertile women with endometriosis, 23% also had a male factor and 41% had a tubal factor.

Table 2 shows that 85.71% of women had dysmenorrhea, mostly mild (41.07%) and moderate (25 %). Twenty cases (35.71%) had the symptom of dyspareunia.

The stage of endometriosis according to the revised ASRM classification at the time of the initial diagnosis by laparoscopy or laparotomy was as follow: nineteen cases (33.93%) were minimal, 22 cases (39.29%) were mild, 10 cases (17.85%) were moderate, and 5 cases (8.93%) were severe. The most common site for endometriotic lesions was the ovaries (57.14%) followed by the tubes (53.57%), cul-de-sac (39.29%), uterus (32.14%), pelvic wall (19.64%), uterosacral ligaments (14.29%), and broad ligaments (3.57%). In many cases there was lesion in more than

one site.

About pregnancy outcome, 5 out of 41 cases (12%) of minimal and mild endometriosis group became pregnant, 2 cases after surgical treatment, 2 cases after medical treatment, and one case with no treatment. In the moderate endometriosis group , there were 2 pregnancies (20%) occurred after medical treatment. No pregnancy occurred in the severe endometriosis group.

Table 1. Characteristics of infertile women with endometriosis

Characteristics	mean ± SD
Age at initial diagnosis (years)	32.55 ± 3.99
BMI (kg/m2)	21.50 ± 3.04
Age at menarche (years)	13.96 ± 1.64
Interval of menstruation (days)	29.84 ± 5.24
Duration of menstruation (days)	4.32 ± 1.44
Duration of infertility (years)	5.79 ± 3.07

Table 2. Symptoms of dysmenorrhea

Dysmenorrhea	Numbers	Percentage
none	8	14.29
mild	23	41.07
moderate	14	25.00
severe	11	19.64
Total	**56**	**100.00**

Discussion

The reported prevalence rates of endometriosis in infertility range from 4.5% to 33% depending on the specific subset of population analysed : infertile women, symptomatic patients, women undergoing tubal sterilization, pelvic surgery (either abdominal or vaginal), or general population.[7,12] But it has been considered high among infertility group. Selection is probably the major potential bias in studies of endometriosis, infertility is often the reason for diagnostic procedures, thus artificial raising the frequency of infertile women among the cases. This study is not the final answer to the question of prevalence of endometriosis in infertility. It contains certain limitations that should be addressed. First, because the diagnosis of endometriosis must be confirmed by directed visualization, usually at laparoscopy or laparotomy, but some infertile women did not accept such surgical procedures. Therefore the investigation is limited to the ones that were clinically diagnosed endometriosis or unexplained infertility. Second, some cases of endometriosis could be missed to be clinically probable or possible endometriosis and treated by experienced physician without histological or visual confirmation.

Among the 56 instances of endometriosis in our infertile women, the infertility was primary in 34 (60.71%). It is relatively low according to previous studies which found that the infertility was primary in 71% and 76%.[8,13] However, it confirmed that the

majority of infertile women with endometriosis were nulliparous as in other studies.[8,9,13] Among secondary infertility group in our study, we found that spontaneous abortion occurred in 8 cases (36.36%) which were higher than normal population as reported in uncontrolled retrospective study.[6] In agreement with the prior report,[10] the mean age of initial diagnosis was 32.55 + 3.99 years. The reason may be that the majority of women with endometriosis and infertility had either mild or no pelvic pain symptoms, so the diagnosis was performed only as a part of infertility evaluation which was rather late.

Although endometriosis is usually considered to be associated with early menarche, frequent menstruations, and long duration of menstruation,[7,9,14,15] our data showed that infertile women with endometriosis had normal menstrual characteristics. This might be due to the number of our sample size.

Interestingly, we observed that the duration of infertility in our study was rather long, with mean time of 5.79 ± 3.07 years. It may be due to the reasons that the frequency of deep dyspareunia and the severity of dysmenorrhea were less in our infertile women, therefore,the treatment was delayed. Second, our institute is the referral center which may be the cause of delayed diagnosis after trial of treatment from another hospitals.

About the pelvic symptoms in our infertile women, dysmenorrhea had occured as high as 85.71%, but were mostly mild. Moreover, we found that the reported frequency of dyspareunia in infertile women with endometriosis was 35.71% which were higher than one study.[10] From this data we can conclude that endometriosis should be suspected in women with subfertility or infertility with pelvic symptoms ie. dysmenorrhea, dyspareunia, or chronic pelvic pain.

About the stage of endometriosis among our infertile women, it had been reported to be minimal or mild in 73.22%, and is consistent with the previous report,[7] but higher than several reports among infertile women with endometriosis which found minimal or mild endometriosis in only 52% and 55%.[8,10] On the other hand, in symptomatic women with endometriosis, the severity of disease is in higher stage than in the infertile group.[1]

The most common site of endometriosis in our study was the ovaries. The second common was the tubes. It is similar to the previous report.[2] This observation has confirmed the notice that the frequency and severity of deep dyspareunia and dysmenorrhea was less in the women with ovarian endometriosis than in those with lesions at other sites. Unlike other study which found that endometriotic lesions were most frequently found in the cul-de-sac and peritoneum.[8] This may be explained by the differrence in study population and severity of endometriosis in fertile women.

Currently, the treatment of infertility in conjunction with endometriosis can be achieved through different methods: medical treatment, surgical treatment and assisted reproductive technology (ART). The choice of treatment for infertile women with endometriosis has been both controversial and complex, largely because of lack of data. The use of revised American Society for Reproductive Medicine classification has limited the overall effectiveness to predict pregnancy.[16] This study found that there was only 5 pregnancies occured among minimal and mild endometriosis group and 2 among moderate group. Our study showed that pregnancy rate to be low because the follow up time was short and some women were lost to follow up after the diagnostic procedures. In addition, there were some infertile women with endometriosis who were also ongoing medical treatment.

In conclusions, the majority of infertile women with endometriosis were nulliparous, had symptoms of dysmennorrhea and dyspareunia. The endometriotic lesions which located at the ovaries and tubes were usually minimal and mild. Laparoscopy should be used to evaluated the clinically diagnosed endometriosis, unexplained infertility, and infertile women with infertility time more than five years.

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GYNAECOLOGY

Pre-Operative Vaginal Douching for Total Abdominal Hysterectomy in Thailand

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ABSTRACT

Objective To assess the practice of pre-operative vaginal douching prior to total abdominal hysterectomy in major hospitals in Thailand.

Design Descriptive study.

Setting university, regional and provincial hospitals.

Subjects 80 major hospitals.

Methods Questionnaires and telephone inquiries.

Results Nearly all (79 of 80) of the hospitals surveyed practiced vaginal douching before total abdominal hysterectomy. Many antiseptic solutions were used including povidone-iodine, chlorhexidine, chlorhexidine with cetrimide and normal saline. Half (39 of 79) of the hospitals also performed vaginal painting immediately prior to surgery. The most common antiseptic used was povidone-iodine.

Conclusion Vaginal douching remains a routine pre-operative procedure for total abdominal hysterectomy in most Thai hospitals despite the lack of scientific evidence proving its effectiveness. Therefore, randomized, controlled trials should be conducted.

Key words: vaginal douching, total abdominal hysterectomy

Total abdominal hysterectomy(TAH) is a common procedure for the treatment of myoma uteri, ovarian tumor, cervical intraepithelial neoplasia of the cervix. In the U.K., in 1992, the estimated rate of hysterectomies by age 55 was about 20%.[1] There are no reports on the annual number of TAHs performed in Thailand.

When performing TAH, the vaginal canal is entered, however, the vaginal canal contains a large and varied suite of bacteria. It is believed that lowering the bacterial count in the vaginal canal will reduce the chances of post-TAH infection, therefore, vaginal douching is recommended as a routine pre-operative procedure.[2,3] After an extensive review of MEDLINE and the Thai medical index, we could not find any studies documenting the effectiveness of vaginal douching to reduce post-TAH infections.

Our study was undertaken to assess the practice of vaginal douching in major hospitals in Thailand.

Materials and methods

From January to March, 1999, questionnaires (or telephone inquiries) were sent to 80 major

hospitals around Thailand to ask about the practice of vaginal douching and the type of antiseptic solutions used in university, regional and provincial hospitals.

Results

A complete response was received from all 80 hospitals.

Vaginal douching was practiced in all but one hospital (Table1). Seventy of 79 (88.6%) of hospitals performed two vaginal douches per patient. The first douche was performed before bed the day before surgery, and the second the morning of surgery. Only 11.4% (9 of 79) of hospitals performed a single vaginal douche (Table 2).

Many types of antiseptic solutions were used for vaginal douching, the most common being Salvon 1:100, the second most common povidone-iodine. Six of 79 hospitals used normal saline solution (Table 3).

Thirty-nine of 79 hospitals (49.4%) also performed vaginal painting immediately before the surgery. The most commonly used antiseptic was povidone-iodine (Table 4).

Table 1. Practice of pre-operative vaginal douching for total abdominal hysterectomy in various hospitals

Types of hospital	No. of hospitals	Vaginal douching	
		Yes	No
University	4	4 (100.0%)	0(0%)
Regional	25	24 (96.0%)	1 (4.0%)
Provincial	51	51 (100.0%)	0(0%)
Total	80	79(98.8%)	1(1.2 %)

Table 2. Frequency and timing of vaginal douching

Vaginal douching	No. of hospitals	Percentage
Single, before bed time	2	2.5
Single, in the morning of the surgery day	7	8.9
Double, before bed time and in the morning	70	88.6
Total	**79**	**100.0**

Table 3. Antiseptic solution used for vaginal douching

Antiseptic solution		No. of hospitals	Percentage
Savlon 1 : 100	(chlorhexedine+cetrimide)	29	36.7
Savlon 1 : 200	"	7	8.9
Savlon 1 : 800	"	3	3.8
Savlon 1 : 1000	"	7	8.9
Betadine	(povidone-iodine)	9	11.4
Hibitane	(chlohexedine)	7	8.9
Normal saline		6	7.6
Dettol (1:200)	(chloroxylenol)	5	6.3
Lactacyd	(lactoserum+lactic acid)	2	2.5

Antiseptic solution	No. of hospitals	Percentage
Benzakonium (1:1000)	1	1.3
Bactyl 0.5%	1	1.3
KMnO4	1	1.3
Lactid acid	1	1.3
Total	**79**	**100.0**

Table 4. Antiseptic solution used for vaginal painting immediately before surgery

Antiseptic	No. of hospitals	Percentage
Betadine	30	76.9
Hibitane	6	15.4
Acriflavin	2	5.1
Dettol	1	2.6
Total	**39**	**100.0**

Discussion

We conducted an extensive search of MEDLINE to find articles on the practice of pre-operative vaginal douching for TAH, but did not find any. Yet, the practice is believed to reduce post-TAH infection.

At our home base, Srinagarind Hospital, Khon Kaen University, about 300 TAHs are performed annually. Pre-operative vaginal douching is routine. Each patient receives two vaginal douches, one the evening prior to surgery, and one the morning before surgery. Savlon 1:1000 is the antiseptic used.

In our survey, pre-operative vaginal douching for total abdominal hysterectomy was performed routinely in nearly all (79 of 80) hospitals, except in one regional hospital.

The most commonly used douching agent, povidone-iodine is a high grade anti-bactericide; active against gram positive and negative bacteria, acid-fast bacilli, fungi and virus. To contrast, normal saline has no bactericidal activity, but the douche mechanically reduces vaginal flora.[4,5]

Amstey and Jones compared douches using povidone-iodine and normal saline solution in patients who underwent vaginal hysterectomy and they found no statistically significant difference in post-operative morbidity.[6]

Onderdonk et al. compared 0.04% acetic acid and 0.3% povidone-iodine for vaginal douching in normal subjects and found povidone-iodine significantly decreased vaginal flora for 24-48 hours after which flora returned to normal or higher than normal levels.[7]

The materials used for vaginal douching are not costly but the procedure is both time-consuming (which has a cost) and discomforting for the patient. The research conducted by Amstey and Jones and Onderdonk et al. suggests that the effectiveness of the practice is debatable. In this era of cost-consciousness and evidence-based medicine, only scientifically tested practices should be supported. Therefore, randomized controlled trials should be conducted to evaluate the effectiveness of vaginal douching as a pre-operative procedure for TAH.

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GYNAECOLOGY

Adjuvant Hysterectomy Followed Radiotherapy in Cervical Cancer

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ABSTRACT

Objective To evaluate the benefits of hysterectomy followed radiotherapy in CA cervix in Reduction of pelvic recurrence and improvement of survival.

Design Retrospective descriptive analysis.

Setting Department of Obstetrics and Gynecology. Bangkok Metropolitan Administration Medical College and Vajira Hospital.

Subjects Sixty patients with cervical cancer stage 1B ,2A and 2B treated with radiotherapy followed by hysterectomy during October 1993 - October 1998.

Main outcomes measurement Residual cancer at the cervix, pelvic recurrence, distant recurrence, survival and complications.

Results The records of sixty patients with cervical cancer were reviewed. They had a mean age of 46.8 $\pm$ 10.0 years and a mean parity of 3.3 $\pm$ 2.4 . Fifty- two patients [86.7 %] were stage 2B ,5 [8.3 %] were stage 2A and 3 [5.0 %] were stage 1 B . Thirty-three patients [55.0 %] were adenocarcinoma (ADCA), 25 [41.7 %] were squamous cell carcinoma (SCC) and 2 [3.3 %] were adenosquamous carcinoma (ADSCC). These patients received XRT in the dose of 4600-5000 cGy and ICRT in the dose of 4000 cGy. Time interval from completion of radiotherapy to hysterectomies were done within a mean time of 49.5 $\pm$16.6 days after complete radiotherapy. All underwent extrafascial hysterectomies (95%) except 3 had modified radical hysterectomies [5.0 %]. Para-aortic lymph nodes dissections was part of the surgical procedure performed on 55 patients [93.3 %] . 24 out of 60 patients [40.0 %] had residual cancer at the cervix (pathologic incomplete response :PIR), four of them had cancer at surgical margins (positive margins). Thirty-six patients [60.0 %] had no residual cancer at the cervix (pathologic complete response : PCR). Five patients [8.3%] had

para-aortic lymph nodes metastases at the time of surgery: 2 in the PCR group and 3 in the PIR group. Unsatisfactory clinical response to radiotherapy and ADCA or ADSCC histologic types was significantly associated with the PIR. With a mean follow up time of 26.6 + 16.3 months [3-64], 4 patients [6.7 %] had pelvic recurrence: 1 [2.8 %] in the PCR group and 1 [5.0 %] in the PIR with completely resected group and 2 [50.0 %] in the positive margins group. Five patients [8.3 %] had new distant recurrence :1 [2.8 %] in the PCR group, 3 [15.0 %] in the PIR with completely resected group and 1 [25.0 %] in the positive margins group. The overall distant metastases was 8.3%[5 patients]. Prognosis of the positive margins group was the worst [recurrent rate = 75.0%], of the PIR with completely resected group was the better [recurrent rate = 30 %] and of the PCR group was the best [recurrent rate = 5.6 %]. Intra-operative complications occurred 6.7 %, post-operation occurred 21.7 % but severe complications occurred 8.3 % and all were completely corrected.

Conclusion Hysterectomy followed radiotherapy in cervical cancer stage 1B$_2$,2A and 2B has some benefits in patients with unsatisfactory clinical response to radiotherapy or in ADCA or ADSCC histologic types .

Key words : adjuvant hysterectomy, cervical cancer, combined therapy

The management of bulky cervical cancer stage 1B$_2$, 2A, 2B was controversial. Most authors recommended radiotherapy as the primary treatment, since radical hysterectomy was not curative.[1-8]

The major problem of radiotherapy alone in these bulky tumor was pelvic recurrence. Durrance, in 1969 , suggested that extrafascial hysterectomy followed radiotherapy would reduce the frequency of pelvic recurrence in these groups.[1] Many authors such as Nelson , Fletcher , Rutledge , Edinger and Gallion agreed with him.[1,2,9-12] Gallion , in 1985, claimed that the incidence of pelvic recurrence reduced from 19 % to 2% and extra-pelvic recurrence from 16 % to 7 % without an increase in treatment-related complications.[9] Some other investigators, however, questioned the validity of this approach, believing that the patients survival would not be improved due to extra-pelvic recurrence but increased morbidity was encountered.[3,13-16]

The purpose of our study was to evaluate the benefits of hysterectomy followed radiotherapy in cervical cancer stage 1B$_2$,2A,2B in reduction of pelvic recurrence and improvement of survival.

Materials and methods

The records of 60 patients with cervical cancer stage 1B$_2$, 2A, 2B treated with radiotherapy followed by hysterectomy at Vajira Hospital during October 1993 and October 1998 were reviewed. These patients were evaluated and staged by the tumor treatment team that composed of gynecologic oncologists , radio-oncologists and pathologists. The patients then received XRT in the dose of 4600- 5000 cGy [23-25 fractions] and ICRT in the dose of 4000 cGy [4 fractions]. Four to six weeks after completion of radiotherapy they were reevaluated and classified as satisfactory response to radiotherapy if the cervix was small, soft, smooth surface and as unsatisfactory response if the cervix was large , firm , irregular , nodular or ulceration. We agreed to do hysterectomy during 6-12 weeks after complete radiotherapy if there were no other conditions that the surgery must be postponed. The surgical specimens were examined by the pathologists and then reviewed by the tumor treatment team . Adjuvant therapy was discussed and given to the patient with risk factors of recurrence such as positive margins or metastases to nodes. The patients were followed-up every 2-3 months in the first two years and every 6 months there after.

The statistics used were : mean with standard deviation for analysis of age , parity of the patients and size of the tumor, : percent for other clinical characteristics , : chi-square test for evaluation of the correlation of clinical factors and outcomes : Kaplan-Meier survival curve for the prognosis of the patients.

Results

The 60 patients included in this study had a mean age of 46.8 ± 10.0 years [29-75] and a mean parity of 3.3 ±2.4 [0-11]. Most of them [52 patients or 86.7 %] were stage 2 B only 5 patients [8.3 %] were stage 2A and 3 [5.0%] were stage 1B$_2$. Thirty-three patients [55.0 %] were adenocarcinoma (ADCA), 25 [41.7 %] were squamous cell carcinoma(SCC) and 2 [3.3 %] were adenosquamous carcinoma (ADSCC) .

The characteristics of tumors were infiltrating type in 38 patients [63.3 %] and exophytic type in 22 patients [36.7 %] The mean diameter of cervical lesions was 4.4 ±0.9 cm [3-6]. Twenty-seven patients [45.0 %] had cervical lesions larger than 4 cm while 33 [55.0 %] were 4 cm or smaller. ADCA group and ADSCC group were smaller than SCC group [4.1±0.7 cm vs. 4.0±0.0 cm vs. 4.8±0.9 cm]. (table 1)

Four to six weeks after complete radiotherapy the patients were reevaluated. 28 patients [46.7 %] were satisfactory clinical response to radiotherapy and 32 patients [53.3 %] were unsatisfactory clinical response. The mean size of the cervix after radiotherapy was 2.9 ± 0.6 cm[3.0-6.0] , 45 patients [75.0 %] had cervical size of 3 cm or larger and 15 [25.0 %] had cervical size of smaller than 3 cm. (table 2)

The mean time interval between complete radiotherapy and surgery was 49.5 ± 16.6 days [27-81]. Fifty-seven patients [95.0 %] underwent extrafascial hysterectomies and 3 patients [5.0 %] had modified radical hysterectomies. Para-aortic lymph nodes dissections were performed in 56 patients [93.3 %]. The mean operative time was 148 ± 29 minutes [60-240] .The mean blood loss was 424 ± 262 ml.[100-1600] and the mean blood transfusion was 0.7 ± 0.8 units [0-4]. Intra-operative complications occurred in 4 patients [6.7 %], 2 had bleeding more than 1000 ml , 1 had injury to the small bowel and another one had injury to the bladder. Post-operative complications occurred in 13 patients [21.7%]. Nine patients had chronic infected and delayed healing of vagina stumps , 2 patients had infected abdominal wounds. More serious complications occurred in 5 patients [8.3 %] ; three were partial gut obstructions, one was leakage of ureter with urenoma and the last one was small vesico-vaginal fistula. All patients with complications were completely corrected. (table 6)

From the pathologic reports of surgical specimens , 36 patients [60.0 %] had no residual cancer at the cervix or pathologic complete response [PCR] but two of them [5.6 %] had para-aortic lymph nodes metastases . There were 24 patients [40.0 %] that had residual cancer at cervix or pathologic incomplete response [PIR] and 20 patients[33.3 %] of this group had been completely resected [PIR with completely resected] but 4 [6.7 %] had cancer at surgical margins (positive margins). Three of the PIR group had para-aortic lymph nodes metastases. (table 3)

Multiple factors were evaluated with the finding that only histologic types of ADCA or ADSCC and unsatisfactory clinical response to radiotherapy were significantly associated with PIR.(table 4)

Patients were followed with a mean time of 26.6 ±16.3 months [3 -62] 4 patients [6.7 %] had pelvic recurrence with a mean time to recurrence of 15.9 ± 9.7 months [6-47] , one [2.8 %] from the PCR group, one [5.0 %] from the PIR with completely resected group , two [50.0 %] from the positive margins group.(table 5)

Three of the five patients with para-aortic lymph nodes metastases[8.3 %] had adjuvant para-aortic radiotherapy and the two from the PCR group had no recurrence for 54 and 64 months of follow-up but the other one from the PIR group had recurrence in 29 months, one patient from the PIR group was

given Megace and recurrence occurred within 21 months, the last one from the PIR group received chemotherapy for 5 course and loss follow up.

Five patients [8.3 %] had distant metastases after surgery, one from the PCR group [1/36 or 2.8 %], three from the PIR with completely resection group [1/20 or 5.0 %] and the last one from PIR with positive margins group [1/4 or 25.0 %].(table 5)

Fifty- four patients [90.0 %] were alive with a mean follow -up time of 27.1 ±16.6 months [3-62]. Six patients [10.0 %] were dead with a mean survival time of 21.6 ± 12.8 months [6-29]. Recurrence free survival times and overall survival times are presented in Figures 1 and 2.

Table 1. Clinical characteristics of the patients

	Patient's characteristics	Number (%)
Number of the patients		60
Age of the patients		46.8 ± 10.0 [29-75] yr.
Parity of the patients		3.3 ± 2.4 [0-11]
Stage of the cancer	1B	3 [5.0 %]
	$2A^2$	5 [8.3 %]
	2B	52 [86.7 %]
Histology of the cancer	ADCA	33 [55.0 %]
	ADSCC	2 [3.3 %]
	SCC	25 [41.7 %]
Characteristics of the tumor	Infiltrating type	38 [63.3 %]
	Exophytic type	22 [36.7 %]
Sizes of the primary tumor	Mean	4.4 ± 0.9 [3.0-6.0] cm.
	ADCA group	4.1 ± 0.7 cm
	SCC group	4.8 ± 0.9 cm
	ADSCC group	4.0 ± 0.0 cm
	size > 4 cm	27 [45.0 %]
	size ≤ 4 cm	33 [55.5 %]

Table 2. Clinical evaluation after radiotherapy

	Clinical evaluation	Number (%)
Clinical response to radiotherapy		
	Satisfactory	28 [46.7 %]
	Unsatisfactory	32 [53.3 %]
Sizes of the cervix (mean)		2.9 ± 0.6 [2-4] cm
	< 3 cm	15 [25.0 %]
	≥ 3 cm	45 [75.0 %]

Table 3. Pathologic reports of surgical specimens

Pathologic reports	Number (%)
No residual cancer at the cervix [PCR]	36 [60.0 %]
-without para-aortic lymph nodes metastases	34
-with para-aortic lymph nodes metastases	2
Residual cancer at the cervix [PIR]	24 [40.0 %]
a) PIR with completely resected	20 [33.3 %]
-without para-aortic lymph nodes metasteses	17
-with para-aortic lymph nodes metastases	3
b) PIR with positive margins	4 [6.7 %]
-without para-aortic lymph nodes metastases	4
-with para-aortic lymph nodes metastases	0
Total	**60**

Table 4. Factors that might predict residual cancer at the cervix

FACTORS	SUBSET (residual)	PIR (%)	PCR (%)	TOTAL (%)	P
A) Stages	-1B +2A	2 [25.0 %]	6 [75.0 %]	8 [13.3 %]	
	-2B[2]	22 [42.3 %]	30 [57.7 %]	52 [86.7 %]	0.35 NS
B) Histology	-SCC	6 [24.0 %]	19 [76.0 %]	25 [41.7 %]	
	-ADCA+ADSCC	18 [51.7 %]	17 [58.6 %]	35 [58.3 %]	0.03 Sig***
C) Characteristics of	-Exophytic	8 [36.4 %]	14 [63.6 %]	22 [36.7 %]	
the tumors	-Infiltrating	16 [42.1 %]	22 [57.9 %]	38 [63.3 %]	0.66 NS
D) Sizes of the	- ≤ 4 cm	16 [50.0 %]	16 [50.0 %]	32 [53.3 %]	0.09 NS
primary tumor	- > 4 cm	8 [28.6 %]	20 [71.4 %]	28 [46.7 %]	
E) Sizes of the	(mean)	4.25 cm	4.51 cm	4.40	0.24 NS
primary tumor					
F) Sizes of the cervix	- < 3 cm	4 [26.7 %]	11 [73.3 %]	15 [25.0 %]	
after radiation	- > 3 cm	20 [44.4 %]	25 [55.6 %]	45 [75.0 %]	0.22 NS
G) Sizes of the cervix	(mean)	3.1 cm	2.8 cm	2.9	0.09 NS
after radiation					
H) Clinical response	-Satisfactory	5 [17.9 %]	23 [82.1 %]	28 [46.7 %]	
to radiation	-Unsatisfactory	19 [59.4 %]	13 [40.6 %]	32 [53.3 %]	0.001 Sig.***

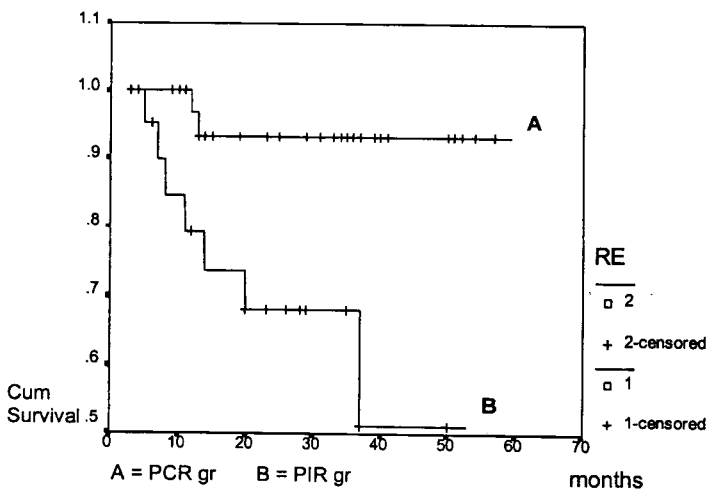
Table 5. Prognosis of the patients

		pelvic recurrence	distant recurrence	para-aortic LN metastases
No residual cancer at cervix	[n=36]	1 [2.8 %] *	1 [2.8 %] **	2 [5.6 %]
Residual cancer at cervix	[n=24]	3 [12.5 %] *	4 [16.7 %] **	3 [12.5 %]
-completely resected	(n=20)	1 (5.0 %)	3 (15.0 %)	3 (15.0 %)
-positive margins***	(n=4)	2 (50.0 %)	1 (25.0 %)	0 (00.0 %)
All patients	[n=60]	4 [6.7 %]	5 [8.3 %]	5 [8.3 %]

* P=0.17 NS ** P=0.07 NS *** one patient loss follow up

Table 6. Operative problems and post-operative complications

	Mean (S.D.)		Range
Time from radiotherapy to surgery	49.5 ± 16.6	days	[27-81]
Operative time	148 ± 29	minutes	[90-240]
Blood loss	424 ± 262	ml.	[100-1600]
Blood transfusion	0.7 ± 0.8	units	[0-4]
	Numbers (%)		
Intra-operative complications	4 [6.7 %]		
-bleeding >1000 ml.	2		
-bowel injury	1		
-bladder injury	1		
Post-operative complications	13 [21.7 %]		
Minor complications	11 [18.3 %]		
-chronic infection of vagina	9		
-wound infection of stumps	2		
Major complications	5 [8.3 %]		
-partial gut obstruction	3		
-leakage of ureter with urenoma	1		
-small vesico-vagina fistula	1		



Kaplan-Meier curve

Fig. 1. Disease free survival (From complete radiotherapy).

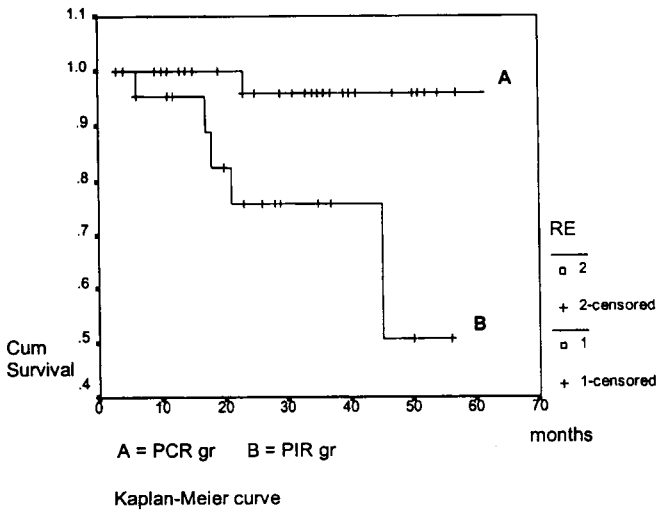


Fig. 2. Overall survival (From complete radiotherapy).

Discussion

The main purpose of hysterectomy followed radiotherapy in the treatment for early-staged bulky cervical cancer is the reduction of pelvic recurrence or persistence of cancer after 6 months.[1,2,9,10,12] Six to twelve weeks after complete radiotherapy is the best time for hysterectomy because the tissue inflammation is subsided and the fibrosis is not so dense, thus minimising complications.[5,17]

Residual cancer at cervix (PIR) is associated with pelvic recurrence while if the cervix has no residual cancer (PCR), pelvic recurrence is unlikely to occur.[2,8,9,12,15] Additional hysterectomy in cases with PCR may be unnecessary and should be omitted. Our suggestion is that the hysterectomy should be reserved only for the patients who still had residual cancer after radiation. However, there was no such tool to accurately detect this entity.

In this study we found that 40.0 % of the patients still had residual cancer while 60% had PCR which was comparable to Murayama's [12] and Gallion's report [9] of 37 and 32.5% respectively Unsatisfactory clinical response to radiotherapy and ADCA or ADSCC histologic types were the two factors that had significant correlation with PIR.

Pelvic recurrence occurred 16-43 % in the patients treated with radiotherapy alone.[9,10,14,16] In this study we used combined therapy and pelvic recurrence occurred 6.7 %[4 pt] nearly the same as 7.0 % of Prempree's report [10] but slightly more than 2 % of Gallion's report.[9] There were only 2.8 % in the PCR group which was less than 12.5 % in the PIR group. In the positive margins group pelvic recurrence occurred for 50.0 % but in the PIR with completely resected group pelvic recurrence occurred only 5.0 %. This may be the support reason of adjuvant hysterectomy after radiotherapy but the surgery should remove all residual cancer.

Distant metastasis is the main reason that many authors object hysterectomy after radiotherapy.[4,13,14,16] In this study we performed para-aortic lymph node dissection in 56 patients and found that 5 patients [8.3 %] had already para-aortic lymph nodes metastases slightly more than 5 % of Maruyama's report.[12] This finding means hysterectomy cannot cure these 5 patients. During follow-up , we found new distant recurrence in 5 patients [8.3 %]. This implied that hysterectomy

alone cannot prevent distant recurrence in 10 patients [16.7 %].

Additional para-aortic lymph nodes dissection in this study was not increasing complications and had a benefit of knowing the extent of cancer but was questionable about the therapeutic benefit because the effective adjuvant treatment of para-aortic nodes metastases was not found. We gave para-aortic radiation (LINAC) to three patients and found that two had no recurrence with follow-up times of 54 and 64 months and the other one had recurrence within 29 months of follow-up. The other two patients refused radiotherapy. One was given Megace (also refused chemotherapy) and recurrence occurred within 21 months. The last one was given chemotherapy (cisplatin+5 FU) and had no progression during chemotherapy but she loss follow-up after the fifth course.

Hysterectomy may be useful in prediction of prognosis because the present of residual cancer at cervix associated with bad outcomes.[9,12] In this study the prognosis of the PCR group is better than that of the PIR group.

Complications of treatment in this study occurred 21.7 % and seem to be higher than other reports[3,9,14] but most of them were minor. The more serious complications occurred only 8.3 % and all were completely corrected.

Conclusively, adjuvant hysterectomy after radiotherapy had some benefits in reduction of pelvic recurrence but it should be used in selective conditions such as unsatisfactory clinical response to radiotherapy and in the patients with ADCA or ADSCC.

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CASE REPORT

Malignant Mixed Mullerian Tumor of Uterus Produced Alpha-fetoprotein

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ABSTRACT

A case of malignant mixed mullerian tumor of the uterus with alpha-fetoprotein (AFP) production in a postmenopausal woman is reported. This patient was initially diagnosed by rising of serum alpha-fetoprotein without any clinical symptoms. After primary surgery tumor rapidly relapsed. Adjuvant treatment by hormonal therapy was not responsive. Finally, tumor seemed to reach partial response (PR) by using platinum compounds with adriamycin. Serum alpha-fetoprotein level was correlated to tumor volume. This is one of the very rare case reports in the literatures.

Uterine sarcoma comprises of 2-5 % of all uterine malignancy.[1-5] Among this, Malignant Mixed Mullerian Tumors (MMMT) of the uterus is considered to be one of the most common. Its histopathology composed of neoplastic epithelial components and mesodermal elements, of which, either or both may show a spectrum of change varying from mild atypia to frank malignancy. Most MMMT patients present with vaginal bleeding. The poor prognosis of MMMT patients may reflect ineffective primary treatment or occult extrauterine spread early in its course. The histogenesis of MMMT remains unclear. To date, there have been only 9 reported cases of MMMT that could produce alpha-fetoprotein in the English literature. We report here a case of MMMT which produced alpha-fetoprotein and got a partial response after platinum and adriamycin treatment.

A 71-year-old Thai female, Para 8-0-0-8, visited Chulalongkorn Hospital in September 1998 for annual check up. She was asymptomatic except for medical history of hepatitis B carrier and ischemic heart disease. No familial history of cancer was noted. Physical examination including pelvic exam was within normal limit. But her serum alpha- fetoprotein was elevated (124.3 IU/ml, normal 0-5.3 IU/ml). Transvaginal ultrasonography disclosed thickening of the endometrium (27mm). Whole abdominal Ultrasonography and CT scan were normal. Endometrial tissue was obtained by fractional curettage. The histopathological specimen revealed malignant mixed mullerian tumor. Provisional diagnosis at that time was malignant mixed mullerian tumor of the uterus. She underwent expolatory laparotomy with surgical staging in September 1998. The operative finding showed a polypoid-like mass (diameter 2.5x1 cm) within the uterine cavity. The final

histopathology confirmed the diagnosis of carcinosarcoma of the endometrium. No myometrial invasion could be demonstrated. The same specimen was also sent for immunohistochemical stained of which was positive for alpha-fetoprotein (figure 1). On the seventh operative day her serum alpha-fetoprotein decreased to 57.1 IU/ml. After counselling with the patient about further treatment no adjuvant therapy was given.

In December 1998, she developed right upper abdominal pain. Abdominal ultrasonography revealed an echogenic mass, size 12x8x9 cm, in subhepatic area. Her alpha-fetoprotein was 32,971 IU/ml. She had second exploratory laparotomy. A solid tumor, diameter 15 cm, located at right hepatic flexure and a 3-cm vaginal cuff tumor were found. Omental seedings were also noted. Right half colectomy, omentectomy with tumor debulking was done. Pathological report was metastatic carcinoma (malignant mixed mullerian tumor). After operation she received adjuvant treatment consisting of carboplatin 300 mg/m^2 and Goserelin acetate (Zoladex) 3.6 mg every 4 weeks. Her alpha-fetoprotein one week and one month after treatment were 7,226 IU/ml and 5,611 IU/ml respectively. The patient continued on chemotherapy for 3 courses until the raised of alpha-fetoprotein was detected (35,826 IU/ml). CT scan of the whole abdomen demonstrated a mass at right lumbar region diameter 15 cm. She was given cisplatin (60 mg/m^2) and adriamycin (60 mg/m^2) every 4 weeks. The patient tolerated the treatment quite well. Her current condition, after 2 courses of this chemotherapeutic regimen, was asymptomatic. Her last serum alpha-fetoprotein, in May 1999, was 22,777 IU/ml. The tumor size was decreased to 10 cm in diameter. The corelation of serum alpha-fetoprotein and clinical course is demonstrated in Diagram 1.

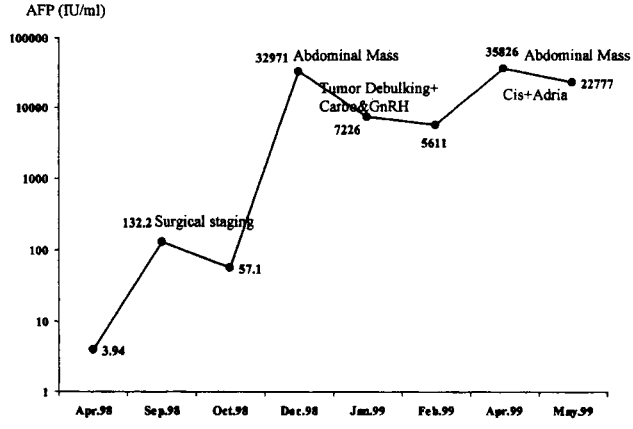

Diagram 1 Corelation of serum alpha-fetoprotein and clinical course.

Discussion

This article aimed to report the case of malignant mixed mullerian tumor produced alpha-fetoprotein. There were less than 10 cases reported in the literatures.[1-4]

Uterine sarcoma accounts for less than 10% of all uterine neoplasm.[5] The malignant mixed mullerian tumor is a mixture of carcinoma and sarcoma. Although any combination is possible, serous carcinoma admixed with endometrial stromal sarcoma is the most common histologic type.[5] The behavior of this type of tumor is aggressive.[5-7] Patients with tumor confined to the uterus at the time of surgery had a 5-year disease-free survival of 52%. When there was extension outside of the uterus, the 5-year disease-free survival dropped to 28%.[6] Treatment of early stage should begin with

surgical resection of primary tumor.[5] Adjuvant treatment after surgery still has no definite benefit to overall survival in early stage.[7-9] Hannigan et al[8] reported no benefit of VAC chemotherapy. The gynecologic oncology group prospectively studied stage I or II uterine sarcoma treated with adriamycin.[10] But no survival improvement was noted. Rose PG[9] reported a decreased recurrence of both pelvic and distant tumor for endometrial sarcoma but not for leiomyosarcoma treated with adjuvant radiation. However, the role of radiotherapy in malignant mixed mullerian tumor seemed to be controversial. In recurrent or advance cases, multiagents chemotherapy were given with overall response rate 18-30% .[11-15] Most of chemotherapeutic agents were cisplatin, adriamycin, ifosfamide and etoposide. Among these, cisplatin showed significant overall response.[16;17] There was a study which reported positive steroid receptor in 50% of the specimens.[18;19] But there were only anecdotal cases which reported hormonal therapy in MMMT.[19-21]

Although abdominal recurrence was the most common pattern[22], as in our case report, lymphatic and hematogenous spread were also common. According to the patient's underlying heart disease, platinum compounds plus GnRH were used for adjuvant treatment without any improvement. Finally, combination chemotherapy consisting of cisplatin and adriamycin showed clinical partial response under close cardiac monitoring.

Alpha-fetoprotein is produced only very little in normal adult tissue.[23] It can be used as a convenient tumor marker, regardless of the type of tumor. It's easily measured in the serum and has a known half-life of 4-6 days. It's an effective marker in germ cell tumor. When present at raised concentrations, provides an accurate means of tumor activity and response to treatment. Occasionally, upper GI tract cancers and ovarian mucinous cystadenocarcinomas of intestinal type express alpha-fetoprotein.[24] Alpha-fetoprotein may express by tumors which seem to be histologically unrelated including lung, renal carcinoma and rhabdomyosarcoma.[23] From what we' ve known, there have been only 9 reported MMMT cases in the English literature that express alpha–fetoprotein.[1-4] The clinical importance of alpha-fetoprotein production in MMMT remains unclear. Some authors suggested that MMMT producing alpha-fetoprotein might exhibit different clinical behavior. On the other hand, elevated alpha- fetoprotein may provide a useful marker for monitoring the treatment of this tumor. Further studies are needed to understand histogenesis and behavior of this special type of MMMT.

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