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Edited by: Fauziah Taib

ENDOMETRIOSIS

• Endometriosis is a gynecological medical condition in which cells from the lining of the uterus (endometrium) appear and flourish outside the uterine cavity, most commonly on the membrane which lines the abdominal cavity. The uterine cavity is lined with endometrial cells, which are under the influence of female hormones. Endometrial-like cells in areas outside the uterus (endometriosis) are

influenced by hormonal changes and respond in a way that is



similar to the cells found inside the uterus. Symptoms often worsen with the menstrual cycle.

• Endometriosis is typically seen during the reproductive years; it has been estimated that endometriosis occurs in roughly 6–10% of women. Symptoms may depend on the site of active endometriosis. Its main but not universal symptom is pelvic pain in various manifestations. Endometriosis is a common finding in women with infertility. There is no cure for endometriosis, but it can be treated in a variety of ways, including pain medication, hormonal treatments, and surgery.

STAGING:

SURGICALLY, ENDOMETRIOSIS CAN BE STAGED I–IV (REVISED CLASSIFICATION OF THE AMERICAN SOCIETY OF REPRODUCTIVE MEDICINE).

Stage I (Minimal)

Findings restricted to only superficial lesions and possibly a few filmy adhesions

Stage II (Mild)

In addition, some deep lesions are present in the cul-de-sac

Stage III (Moderate)

1, II plus presence of endometriomas on the ovary and more adhesions

Stage IV (Severe)

1, II & III, plus extensive adhesions

Localization



Most endometriosis is found on these structures in the pelvic cavity

- Ovaries (the most common site)
- Fallopian tubes
- The back of the uterus and the poste-

rior cul-de-sac

- The front of the uterus and the anterior cul-de-sac
- Uterine ligaments such as the broad or round ligament of the uterus
- Pelvic and back wall
- Intestines, most commonly the rectosigmoid

- Urinary bladder and ureters

Bowel endometriosis affects approximately 10% of women with endometriosis, and can cause severe pain with bowel movements.

Causes, incidence, and risk factors

Every month, a woman's ovaries produce hormones that tell the cells lining the uterus (womb) to swell and get thicker. The body removes these extra cells from the womb lining (endometrium) when you get your period.

If these cells (called endometrial cells) implant and grow outside the uterus, endometriosis results. The growths are called endometrial tissue implants. Women with endometriosis typically have tissue implants on the ovaries, bowel, rectum, bladder, and on the lining of the pelvic area. They can occur in other areas of the body, too.

Unlike the endometrial cells found in the uterus, the tissue

implants outside the uterus stay in place when you get your period. They sometimes bleed a little bit. They grow again when you get your next period. This ongoing process leads to pain and other symptoms of endometriosis.

The cause of endometriosis is unknown. One theory is that the endometrial cells shed when you get your period travel backwards through the fallopian tubes into the pelvis, where they implant and grow. This is called retrograde menstruation. This backward menstrual flow occurs in many women, but researchers think the immune system may be different in women with endometriosis.

Endometriosis is common. Sometimes, it may run in the family. Although endometriosis is typically diagnosed between ages 25 - 35, the condition probably begins about the time that regular menstruation begins.

Risk factors of develop endometriosis includes:

- Family history of endometriosis
- Started your period at a young age
- Never had children
- Have frequent periods or they last 7 or more days
- Closed hymen, which blocks the flow of menstrual blood during the period

Call for an appointment with your health care provider if:

- You have symptoms of endometriosis
- Back pain or other symptoms come back after endometriosis is treated

Pathophysiology

While the exact cause of endometriosis remains unknown, many theories have been presented to better understand and explain its development. These concepts do not necessarily exclude each other. The pathophysiology of endometriosis is likely to be multifactorial and to involve an interplay between several factors.

Broadly, the aspects of the pathophysiology can basically

be classified as underlying predisposing factors, metabolic changes, formation of ectopic endometrium, and generation of pain and other effects. It is not certain, however, to what degree predisposing factors lead to metabolic changes and so on, or if metabolic changes or formation of ectopic endometrium is the primary cause. Also, there are several theories within each category, but the uncertainty over

what is a cause versus what is an effect when considered in relation to other aspects is as true for any individual entry in the pathophysiology of endometriosis.

Also, pathogenic mechanisms appear to differ in the formation of distinct types of endometriotic lesion, such as peritoneal, ovarian and rectovaginal lesions.

Signs and symptoms

1. Pelvic pain

A major symptom of endometriosis is recurring pelvic pain. Symptoms of endometriosis-related pain may include:

- dysmenorrhea – painful, sometimes disabling cramps during menses; pain may get worse over time (progressive pain), also lower back pains linked to the pelvis
- chronic pelvic pain –

typically accompanied by lower back pain or abdominal pain

- dyspareunia – painful sex
- dysuria – urinary urgency, frequency, and sometimes painful voiding

2. Fertility

Many women with infertility may have endometriosis. As endometriosis can lead to anatomical distortions and adhesions (the fibrous bands that form between tissues and or-

gans following recovery from an injury), the causality may be easy to understand; however, the link between infertility and endometriosis remains enigmatic when the extent of endometriosis is limited

3. Other

Other symptoms include constipation and chronic fatigue

Note: There may be no symptoms. Some women with a large number of tissue implants in their pelvis have no pain at all, while some women with milder disease have severe pain.

DIAGNOSIS

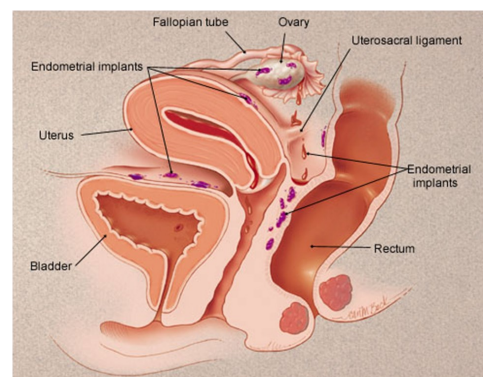
A health history and a physical examination can in many patients lead the physician to suspect endometriosis. Laparoscopy, a surgical procedure where a camera is used to look inside the abdominal cavity, is the gold standard in diagnosis. However, in the United States most insurance plans will not cover surgical diagnosis unless the patient has already attempted to become pregnant and failed.

Use of imaging tests may identify endometriotic cysts or larger endometriotic areas. It also may identify free fluid often within the Recto-uterine pouch. The two most common imaging tests are ultrasound and magnetic resonance imaging (MRI). Normal results on these tests do not eliminate the possibility of endometriosis. Areas of endometriosis are often too small to be seen by these tests. The only way to diagnose endometriosis is by laparoscopy or other types of surgery with lesion biopsy. The diagnosis is based on the characteristic appearance of the disease, and should be corroborated by a biopsy. Surgery for diagnoses also allows for surgical treatment of endometriosis at the same time.

Etiology: Theories

- Sampson: "Retrograde Menstruation"
- Hematologic Spread
- Lymphatic Spread
- Coelomic Metaplasia
- Genetic Factors
- Immune Factors
- Combination of the Above

No Single Theory Explains All Cases of Endometriosis



Expectations (prognosis)



Proper counseling of patients with endometriosis requires attention to several aspects of the disorder. Of primary importance is the initial operative staging of the disease to obtain adequate information on which to base future decisions about therapy.

The patient's symptoms and desire for childbearing dictate appropriate therapy. Not all therapy works for all patients. Some patients have re-

occurrences after surgery or pseudomenopause. In most cases, treatment will give patients significant relief from pelvic pain and assist them in achieving pregnancy.

It is important for patients to be continually in contact with their physician and keep an open dialog throughout treatment. This is a disease without a cure but with the proper communication, one with endo-

metriosis can attempt to live a normal, functioning life.

Recurrence:

The underlying process that causes endometriosis may not cease after surgical or medical intervention, and the annual recurrence rate is given as 5–20 % per year reaching eventually about 40% unless hysterectomy is performed or menopause reached.

*Get to know the
management of
Endometriosis*

Management

While there is no cure for endometriosis, in many women menopause (natural or surgical) will abate the process. In patients in the reproductive years, endometriosis is merely managed: the goal is to provide pain relief, to restrict progression of the process, and to restore or preserve fertility where needed. In younger women with unfulfilled reproductive potential, surgical treatment attempts to remove endometrial tissue and preserving the ovaries without damaging normal tissue.

In general, the diagnosis of endometriosis is confirmed during surgery, at which time ablative

steps can be taken. Further steps depend on circumstances: patients without infertility can be managed with hormonal medication that suppress the natural cycle and pain medication, while infertile patients may be treated expectantly after surgery, with fertility medication, or with IVF.

Sonography is a method to monitor recurrence of endometriomas during treatments



Treatments



Birth control pills may help to prevent or slow down the development of the endometriosis.

Treatments for endometriosis in women who do not wish to become pregnant include:

1. Hormonal medication

- Progesterone or Progestins: It counteracts estrogen and inhibits the growth of the endometrium. Such therapy can reduce or eliminate menstruation in a controlled and reversible fashion. Progestins are chemical variants of natural progesterone.

- Avoiding products with xenoestrogens, which have a similar effect to naturally produced estrogen and can increase growth of the endometrium.

- Hormone contraception therapy: OCPs reduce menstrual pain associated with endometriosis. They may function by reducing or eliminating menstrual flow and providing estrogen support. Typically, it is a long-term approach. Recently Seasonale was FDA approved to reduce periods to 4 per year. Other OCPs have however been used like this off label for years. Continuous hormonal contraception consists of the use of combined oral contraceptive pills without the use of placebo pills, or the use of NuvaRing or the contraceptive patch without the break week. This eliminates monthly bleeding episodes.

- Danazol (Danocrine) and gestrinone are suppressive steroids with some androgenic activity. Both agents inhibit the growth of endometriosis but their use remains limited as they may cause hirsutism and voice changes.

- Gonadotropin Releasing Hormone (GnRH) agonist: These agents work by increasing the levels of GnRH. Consistent stimulation of the GnRH receptors results in downregulation, inducing a profound hypoestrogenism by decreasing FSH and LH levels. While effective in some patients, they induce unpleasant menopausal symptoms, and over time may lead to osteoporosis. To counteract such side effects some estrogen may have to be given back (add-back therapy). These drugs can only be used for six months at a time.

- Lupron depo shot is a GnRH agonist and is used to lower the hormone levels in the woman's body to prevent or reduce growth of endometriosis. The injection is given in 2 different doses: a 3 month course of monthly injections, each with the dosage of (11.25 mg); or a 6 month course of monthly injections, each with the dosage of (3.75 mg).

- Aromatase inhibitors are medications that block the formation of estrogen

and have become of interest for researchers who are treating endometriosis.

2. Other medication:

- NSAIDs: Anti-inflammatory. They are commonly used in conjunction with other therapy. For more severe cases narcotic prescription drugs may be used. NSAID injections can be helpful for severe pain or if stomach pain prevents oral NSAID use.

- Opioids: Morphine sulphate tablets and other opioid painkillers work by mimicking the action of naturally occurring pain-reducing chemicals called "endorphins". There are different long acting and short acting medications that can be used alone or in combination to provide appropriate pain control.

- Following laparoscopic surgery women who were given Chinese herbs were reported to have comparable benefits to women with conventional drug treatments, though the journal article that reviewed this study also noted that "the two trials included in this review are of poor methodological quality so these findings must be interpreted cautiously. Better quality randomised controlled trials are needed to investigate a

Continue....

possible role for CHM [Chinese Herbal Medicine] in the treatment of endometriosis."

•Pentoxifylline: a phosphodiesterase inhibitor, has a proposed action of inhibiting the production of inflammatory cytokines as well as inhibiting the activation of immune cells in peritoneal fluid, thereby decreasing pain from endometriosis and improving fertility. On systematic review by the Cochrane Collaboration, randomized controlled trials have shown a trend towards improving pregnancy rates with pentoxifylline treatment (odds ratio of 1.54, 95% CI 0.89-2.66)

and a decreasing trend in pain scores with treatment (mean difference -1.60, 95% CI -3.32-0.12). However, neither of these outcomes reached statistical significance on analysis.

•Angiogenesis inhibitors lack in clinical evidence of efficacy in endometriosis therapy.

Under experimental *in vitro* and *in vivo* conditions, compounds that have been shown to exert anti-angiogenic effects on endometriotic lesions include growth factor inhibitors, endogenous angiogenesis inhibitors, fumagillin analogues, statins, cyclo-oxygenase-2 inhibitors, phytochemical compounds,

modulators, dopamine agonists, peroxisome proliferator-activated receptor agonists, progestins, danazol and gonadotropin-releasing hormone agonists.

3. Surgery:

Procedures are classified as:

- conservative when reproductive organs are retained,
- semi-conservative when ovarian function is allowed to continue

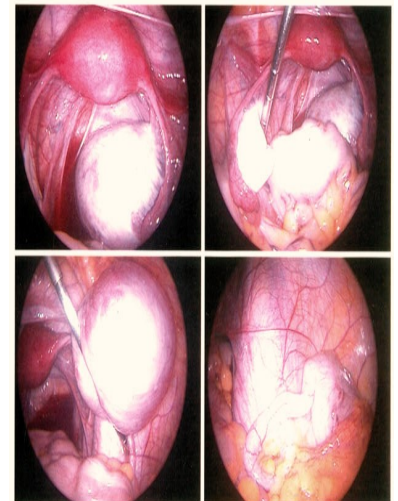
COMPLICATIONS

Endometriosis can lead to problems getting pregnant (infertility). Not all women, especially those with mild endometriosis, will have infertility. Laparoscopy to remove scarring related to the condition may help improve your chances of becoming pregnant. If it does not, fertility treatments should be considered.

Other complications of endometriosis include:

- Long-term (chronic) pelvic pain that interferes with social and work activities
- Large cysts in the pelvis (called endometriomas) that may break open (rupture)

In a few cases, endometriosis implants may cause blockages of the gastrointestinal or urinary tracts. This is rare.



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ADVERSE DRUG REACTION HOSPITAL SEGAMAT Mei-Ogos 2013

DATE	MEDICATIONS	ADR	TREATMENT	REPORTER
15.5.2013	Terazosin 2 mg	Patient previously was on Rasin® 2mg on. Patient complained of discomfort, sometimes pain during urination after a few days switching to Terasin® 2mg on	Symptoms resolved after patient stopped taking Terasin® and took Rasin® 2mg on that he bought from outside pharmacy	Ms Khoo Chee Shin
30.5.2013	Chlorpromazine 100mg	Patient feels dizzy, headache and sleepless night throughout the duration the medication was taken. Effects was since after patient was changed from chlorpromazine 100mg by <i>Idaman Pharma</i> to <i>Atlantic lab</i> (manufacturer)	Changed to patient's older medication	Ms Geethan Chali
4.6.2013	Chlorpromazine 100mg	Headache, dizziness, vomit (non-stop), patient switched from older medication (chlorpromazine by idaman pharma) to the newer one and symptoms started	Stopped taking medication	Ms Geethan Chali
13.6.2013	Terazosin 2 mg	Shortness of breath, pain from head to shoulder, joint pain	.	Ms Josephine
13.6.2013	Metochlorpramide 10mg tds	Oculogyric crisis, stiffness of neck, neck pain + blurring of vision after taking metochlorpramide (maxolon) from GP.	Syr Diphenhydramine	Dr Nasiruddin
17.6.2013	BCG	BCG lymphadenitis at 2 months old, left axilla 0.5cmx0.5cm	Syrup Erythromycin	Dr Intan
12.7.2013	Simvastatin 40mg	Increased LFT parameters and CK levels; diagnosed as acute hepatitis with myositis; patient complained of myalgia, but decreased after stopping simvastatin since 8 julai 2013	Stop taking Simvastatin 40mg	Ms.Khoo Chee Shin
15.7.2013	BCG	Left axillary swelling about 3cmx4cm at 3 months old; consistent with BCG lymphadenitis	Nil	Dr Intan
07.8.2013	IV Ceftriaxone 2g	Developed neck swelling, SOB, chills & rigors, BP dropped to 84/46 mmHg	IV Adrenaline 0.5mcg, IV Chlorpheniramine 10mg stat, IV Hydrocortisone 200mg stat	Dr Sharifah
16.8.2013	IV cefuroxime 750mg stat	Developed macule-papular lesions over face, bilateral upper & lower limbs, back & abdomen; burning sensation	IV Hydrocortisone 100mg, IV Chlorpheniramine 10mg	Dr Nik Mariam

CIPRAM® (CITALOPRAM HYDROBROMIDE): ABNORMAL HEART RHYTHMS ASSOCIATED WITH DOSES MORE THAN 40MG PER DAY

By Lee Sing Chet

Two studies were compared to assess the effects of doses of citalopram and its active S-isomer escitalopram (Lexapro®) on the QT interval in adults. The studies showed that citalopram causes dose-dependent QT interval prolongation that is clinically significant with the 60mg daily dose. Additionally, there is no added effectiveness of citalopram at 60mg/day compared to 40mg/day.¹

MADRAC in its 127th meeting, concluded that the benefits of citalopram continue to outweigh their risks. However, healthcare professionals are reminded that **the maximum daily dose for citalopram is 40mg.**²

LF Asia (Malaysia) Sdn Bhd, the innovator product holder for citalopram, is currently updating the local package insert with the new recommendations on dosing and QT interval prolongation. These safety updates will be extended to all generic products.

Comparatively, for escitalopram, a dose dependent increase in QT interval was seen particularly with 30mg/day when given to healthy volunteers at doses of 10mg and 30mg. When used below **20mg (maximum dose)** which is indicated for major depressive disorder, escitalopram showed substantially lower risk for QT prolongation.

There are **no safety information changes planned for escitalopram** at this time. Nevertheless, escitalopram should also be used with caution in patients with pre-existing cardiac disease. **Table 3** shows the comparative differences between citalopram and escitalopram.

Healthcare professionals should be cautious when prescribing citalopram to patients who have a higher risk of developing prolongation of QT interval including those who have congestive heart failure, bradyarrhythmias, predisposition to hypokalemia, hypomagnesemia and those who are concurrently taking medicines that can prolong QT interval. Any adverse events associated with citalopram and its analogues should be reported to the National Centre for Adverse Drug Reactions Monitoring.

Table 3: Comparison of Citalopram with Escitalopram

	Citalopram ³	Escitalopram ⁴
Indication	Treatment of depression and prevention of depression relapse/recurrence. It is also indicated for panic disorder with or without agoraphobia and obsessive-compulsive disorder.	Treatment of major depressive episodes, panic disorder with or without agoraphobia, social anxiety disorder (social phobia), generalised anxiety disorder and obsessive-compulsive disorder.
Recommended Dose	20-40mg daily	10-20mg daily
Pharmacodynamics	Citalopram is a very Selective Serotonin Reuptake Inhibitor (SSRI) with no, or minimal, effect on noradrenaline (NA), dopamine (DA) and gamma aminobutyric acid (GABA) uptake. It enhances serotonergic activity in the central nervous system (CNS) as a result of its inhibition of serotonin (5-HT) reuptake in CNS neurons. It has no or very low affinity for a series of receptors including 5-HT 1A, -HT2, DA D1 and D2 receptors, α 1-, α 2-, β -adrenoceptors, histamine H 1 muscarine cholinergic, benzodiazepine and opioid receptors.	Escitalopram is the S-enantiomer of the racemate (citalopram) and is the enantiomer to which the therapeutic activity is attributed. Pharmacological studies have shown that the R-enantiomer is not inert but counteracts the serotonin-enhancing and consequent pharmacological properties of the S-enantiomer.
Pharmacokinetics	<p>Absorption: T_{max}: 3 hours Effect of food: no effect</p> <p>Distribution: V_d: 12-17 L/kg</p> <p>Biotransformation: Liver: Metabolised to the active demethylcitalopram, didemethylcitalopram, citalopram-N-oxide and an inactive deaminated propionic acid derivative. The biotransformation of citalopram to demethylcitalopram is mediated by CYP2C19 (approx. 38%), CYP3A4 (approx. 31%) and CYP2D6 (approx.31%).</p> <p>Elimination: T_{1/2}: 1 ½ days</p> <p>Excretion: Liver: 85% Kidney: 15%</p>	<p>Absorption: T_{max}: 4 hours Effect of food: no effect</p> <p>Distribution: V_d: 12-26 L/kg</p> <p>Biotransformation: Liver: Metabolised to the demethylated and didemethylated metabolites, mediated primarily by CYP2C19. Some contribution by the enzymes CYP3A4 and CYP2D6 is possible.</p> <p>Elimination: T_{1/2}: 30 hours</p> <p>Excretion: Liver Kidney</p>

	Citalopram ³	Escitalopram ⁴
Local Products	There are 10 citalopram-containing products registered in Malaysia. A total of 3 strengths are available, namely 10mg, 20mg and 40mg.	For escitalopram, there are 11 registered products, which are available in 4 strengths, i.e. 5mg, 10mg, 15mg and 20mg.
National Centre for ADR Reporting in Malaysia's Database	Since year 2000: No ADR reports received.	Since year 2004: Supraventricular tachycardia: 1 (dose: 30mg)
WHO Vigibase*	Report since year 1989: <ul style="list-style-type: none"> • QT prolonged: 357 • Torsade de pointes: 152 • Ventricular tachycardia: 66 • Supraventricular tachycardia: 27 	Report since year 2003: <ul style="list-style-type: none"> • QT prolonged: 140 • Torsade de pointes: 29 • Ventricular tachycardia: 34 • Supraventricular tachycardia: 17

**WHO Vigibase is a global individual case safety report (ICSR) database system which is contributed by more than 80 member countries worldwide, including Malaysia. The information comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases and it does not represent the opinion of WHO.*

Reference:

1. FDA Drug Safety Communication: Revised recommendations for Celexa (citalopram hydrobromide) related to a potential risk of abnormal heart rhythms with high doses. <http://www.fda.gov/Drugs/DrugSafety/ucm297391.htm> [28 March 2012]
2. Summary report for Citalopram. MADRAC 127 (April 2012).
3. Cipram (citalopram hydrobromide) Package Insert. Malaysia. [May 2012]
4. Lexapro Package Insert. Malaysia. [15 Sept 2008 based on Core SPC ESC 26 Feb 2007]

FDA DRUG SAFETY UPDATES

FDA requires label changes to warn of risk for possibly permanent nerve damage from antibacterial fluoroquinolone drugs taken by mouth or by injection

The U.S. Food and Drug Administration (FDA) has required the drug labels and Medication Guides for all fluoroquinolone antibacterial drugs be updated to better describe the serious side effect of peripheral neuropathy. This serious nerve damage potentially caused by fluoroquinolones (see Table for a list) may occur soon after these drugs are taken and may be permanent.

The risk of peripheral neuropathy occurs only with fluoroquinolones that are taken by mouth or by injection. Approved fluoroquinolone drugs include levofloxacin (Levaquin), ciprofloxacin (Cipro), moxifloxacin (Avelox), norfloxacin (Noroxin), ofloxacin (Floxin), and gemifloxacin (Factive). The topical formulations of fluoroquinolones, applied to the ears or eyes, are not known to be associated with this risk.

If a patient develops symptoms of peripheral neuropathy, the fluoroquinolone should be stopped, and the patient should be switched to another, non-fluoroquinolone antibacterial drug, unless the benefit of continued treatment with a fluoroquinolone outweighs the risk. Peripheral neuropathy is a nerve disorder occurring in the arms or legs. Symptoms include pain, burning, tingling, numbness, weakness, or a change in sensation to light touch, pain or temperature, or the sense of body position. It can occur at any time during treatment with fluoroquinolones and can last for months to years after the drug is stopped or be permanent. Patients using fluoroquinolones who develop any symptoms of peripheral neuropathy should tell their health care professionals right away.

FDA will continue to evaluate the safety of drugs in the fluoroquinolone class and will communicate with the public again if additional information becomes available.

Table. List of approved fluoroquinolone drug products

Generic name	Contained in Brand name
levofloxacin	Levaquin
ciprofloxacin	Cipro
moxifloxacin	Avelox
norfloxacin	Noroxin
ofloxacin	Floxin
gemifloxacin	Factive

FUTHER READING:

FDA Drug Safety Communication: FDA requires label changes to warn of risk for possibly permanent nerve damage from antibacterial fluoroquinolone drugs taken by mouth or by injection. <http://www.fda.gov/Drugs/DrugSafety/ucm365050.htm> [released 15/8/2013]

Pharmacy Night

JOHORE 2013



Pharmacy Night, Johore 2013 was held at Dewan Sangkar Kristal, Johor Bahru



Photo session of pharmacy staff, Hospital Segamat at the end of the dinner.

Performance on the night includes:

- 'Cups' performance with song of "when I'm gone"
- Song of 'Kau ilhamku'



ANNOUNCEMENT

WELCOME TO DEPARTMENT OF PHARMACY

Pegawai Farmasi U41 (FRP)
SOH PEI CIN

Pegawai Farmasi U41 (PRP)
TAI ANN NNY
TEH KENG LONG
TERENCE TAN JIA JUN
GUOK LEEN



CONGRATULATION



Siti Asmah Bt.
Basimin for her
newnborn baby

