MECHANISM OF ACTION OF
EMERGENCY CONTRACEPTIVE PILL

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ABSTRACT

The number of unwanted pregnancies has not decreased in recent years and this should be addressed. Emergency contraception may be effective when used correctly having the advantage that it can be used after an episode of unprotected sexual intercourse (when regular contraception has failed or was not used).

In this research project I set out to explore some of the major reasons why there are still many unwanted pregnancies in Australia. I decided to focus on the use and non-use of emergency contraception, e.g. emergency contraception pill (ECP) “method failures” are not well understood because the actual mechanisms of action are still unclear. There is evidence ECP can effectively interfere with follicle growth and ovulation. It is much less clear is whether ECP is able to interfere with fertilization and implantation, in a way, which may make it acceptable to those who have strong religious beliefs in fertilization being the start of new life.

Emergency contraception has the potential to prevent many unwanted pregnancies when unprotected intercourse has occurred. It has relatively high efficacy in many studies, but true method failures are not well understood. By contrast, many unwanted pregnancies occur for “social reasons” where emergency contraception has not been used. I set out to
study changes in knowledge and usage of emergency contraception in these groups of Australian women seeking termination of pregnancy:
1. Before a dedicated emergency contraception pill (ECP) pack (Postinor) became available in Australia
2. One year after dedicated ECP became available on prescription
3. One year after the ECP pack became available “over the counter” without prescription.

Ninety-nine women were recruited during their presentation with a request for ECP at the six Family Planning Clinics in Australia. All women took LNG 1.5mg in a single dose during the clinic consultation. A blood sample was taken immediately prior to ingestion of the ECP for estimation of serum LH, oestradiol and progesterone levels to calculate the day of the menstrual cycle. Based on these endocrine data we estimated the timing of ovulation to within a ±24-hour period with an accuracy of around 80%. Women were followed up 4-6 weeks later to ascertain pregnancy status. The effectiveness of ECP when taken before and after ovulation was determined.

Three women in this study became pregnant despite taking the ECP (pregnancy rate 3%). All three women who became pregnant had unprotected intercourse between day -1 and 0 and took the ECP on day +2, based on endocrine data. Day zero was taken as ovulation day. Among seventeen women who had intercourse in the fertile period of the cycle and took the ECP after ovulation occurred (on day +1 to +2) we
could have expected 3 or 4 pregnancies, based on Wilcox et al data. Three pregnancies were observed. Among 34 women who had intercourse on days –5 to –2 of the fertile period, and took ECP before or around ovulation, four pregnancies could have been expected, but none were observed. The major discrepancies between women’s self-report of stage of the cycle and the dating calculation based on endocrine data were observed in this study.

These data are supportive of the concept that the LNG ECP has little or no effect on post-ovulation events, but is highly effective before ovulation. Our interpretation of the data in terms of timing of treatment relative to ovulation may explain why EC with LNG works sometimes and fails at other times. A larger study is needed to prove this hypothesis.

To investigate other reasons for such a high rate of unwanted pregnancy, which probably has a larger impact we looked into women’s knowledge of and attitude towards ECP.

Seven hundred and eighteen women participated in this study by answering a questionnaire consisting of 15 questions on their demographic and reproductive characteristics as well as the knowledge about the ECP, e.g. 208 women were enrolled before the ECP was marketed in Australia in 2001, 308 after it was marketed and 202 after it became available over the counter (Group 1, 2, and 3, respectively).
We found that the participants who have heard about ECP were significantly younger (p<0.005). The mean age of women who have never heard about of ECP was 29.8 years compared to 26.3 years in women who have heard about ECP. More women were aware about the ECP after it became available over the counter. Women in group 2 had higher educational level in comparison to women in group 2 and 3 (p<0.005). There was significant trend in increased use of ECP in women of higher educational level (p<0.005). The use of ECP did not increase significantly with improved availability and access to the ECP amongst women presenting for termination of pregnancy.

Wider availability of the ECP pack in Australia and an easier access to it has increased women's awareness about the ECP. However, the use of ECP has not increased.

This study provides better understanding of mechanism of action of LNG ECP and an explanation to the method failure. It also reveals poor knowledge about ECP despite its wider availability and accessibility. Improving these is a worldwide challenge for family planners and all health professionals.
1. INTRODUCTION

1.1 Mechanism of action of levonorgestrel emergency contraception pill

A. Introduction

The rates of unplanned and unwanted pregnancies have not decreased in recent decades in most countries despite various efforts to achieve this [1]. The emergency contraception pill (ECP) is one of the last resorts in avoiding unwanted pregnancy and this has been available in one form or another to women in many countries for a few decades. Surprisingly, despite extensive research in reproductive medicine we still do not know exactly how emergency contraception works. Some evidence points towards interference with follicular growth and function, ovulation, migration and function of spermatozoa, fertilisation, implantation, and endometrial function although the importance of each mechanism is unclear (3). There are increasing data to indicate that high dose, short duration LNG is particularly effective as an ECP by interrupting follicular development and ovulation [2, 3]. An important outstanding question is whether it has any effect on fertilization or implantation. Recent studies in rats and cebus monkeys have convincingly demonstrated no effect of high dose LNG on post-fertilization events in these species [4, 5]. This would have important implications for individuals who believe that independent new life begins at fertilization.
B. Hypothesis

That high dose of LNG ECP acts by interfering with ovulation, but does not have any effect after fertilisation.

Proving this hypothesis would allow ECP to be available for women who would not otherwise use medications that interfere with pregnancy after fertilisation has occurred, because of their religious beliefs. Overall, the ECP is an effective method of preventing pregnancy, with failure rates from 0.5% to 2.5% depending on timing between intercourse and its intake [6]. However, the use of this method is still limited in extent in most countries, including Australia.

C. Aims

- To investigate the efficacy of LNG taken pre-ovulation and post-ovulation

- To precisely identify the time of ECP ingestion in relation to the occurrence of ovulation

1.2 Changes in knowledge and attitudes towards use of emergency contraception pill in abortion seekers as emergency contraception pill became widely available in Australia
A. Introduction

An investigation of knowledge and attitudes towards use of ECP in abortion seekers and their actual use of the method is one means of exploring the limitations of ECP use by women and possible ways to improve it. It has been argued that “over the counter” availability of an ECP pack would contribute to its wider and more timely use and, therefore, would assist in reduction of unplanned pregnancies. Looking into changes in knowledge and attitudes towards ECP since it became available in Australia “over the counter” could help to reveal factors that could be targeted to improve use of ECP.

C. The hypothesis

My second hypothesis is that wider availability of the ECP through a doctor’s prescription would be associated with an increased knowledge and use of ECP, and subsequent availability “over the counter” would be followed by a further increase in knowledge and usage.

C. The aims

- to investigate the knowledge of and attitudes towards emergency contraception of women having induced abortions as LNG ECP became more readily available in Australia through marketing approval (by the therapeutic Goods Administration) and then over the counter
2. LITERATURE REVIEW ON THE EMERGENCY CONTRACEPTION

2.1. Introduction

The ECP can be used to prevent pregnancy after an episode of unprotected sexual intercourse. Unwanted or unplanned pregnancy remains extremely common and many of these are terminated by medical or surgical abortion. Worldwide about 50 million pregnancies are terminated each year [7]. It has been estimated that emergency contraception (EC) could have prevented about half of all induced abortions if it was widely and easily available and women had good information about its use (WHO, 2001).

2.2 History of contraception

Ancient experience

The concept of administering a contraceptive device or using some specific technique after unprotected intercourse in order to prevent pregnancy is very old. A need for fertility regulation arose once the first urban civilizations and settled agriculture were established. Puberty began earlier and breastfeeding was often shortened and supplementary food was introduced earlier than in hunter-gatherer societies, which lead to increased fertility. In prehistoric societies probable fertility rates were 4-6 per 100 women [8]. In modern society a woman would expect to have about ten children. At the same time with a
lower perinatal and childhood morbidity and mortality all of the children would
survive leading to rapid increase of population. Therefore contraception
technique became very important.

Records of contraceptive methods were found in such ancient manuscripts like
Egyptian Ebers Papyrus (1550 BC), the Latin works of Pliny and Elder (23-79
AD), Dioscides (De Materis medica, C 58 to 64 AD), and the Greek writings of
Soramus (Gynecology, C 100 D) [9]. Early attempts to develop contraceptive
techniques involved application of chemical agents within the vagina or physical
methods with a purpose to eliminate spermatozoa from reproductive tract. The
Kahun Papyrus, an Egyptian treatise on Gynaecology of that time (16th to 17th
Century BC), mentions such contraceptive methods as the use of a vaginal
suppository containing crocodile dung mixed with honey and sodium carbonate.
In the Papyrus of Ebers, another document on the ancient Egyptian concept of
medicine and physiology, the recommended method was to insert into the
vagina acacia tips containing Arabic gum which, when dissolved in water,
liberated lactic acid, - not unlike some of the present day contraceptive jellies
containing lactic acid. Postcoital methods of contraception like douching and
jumping up and down after a sexual intercourse were described and practiced
as well. In the available literature to other ancient cultures, such as Indian
medicine, references to contraceptives are conspicuous by their absence,
presumably because the population growth at that time was not alarming, and the pressure on the land was not too great [9].

It is reported that Roman women used the following means of contraception:

1. To insert into “the mouth of the womb” a plug of lint.

2. To smear the cervix with rancid oil or honey or a decoction of cedar oil.

3. To introduce into the vagina an astringent pessary.

Aetius of Amida (500-550) of Mesopotamia, who studied medicine in Alexandria and eventually settled down in Constantinople, recommended the use of contraceptive methods only in those cases where pregnancy jeopardized the life of the woman. To prevent contraception, he advised smearing of the cervical os with honey, opabalsam, etc. It is also mentioned that he prescribed pessaries to bring about sterility but the details of these prescriptions are not known.

**Developments in contraception during industrialization**

During the Medieval period in Europe, the subject of contraception was neglected till about the 16th century. There were some publications in America after 1880 discussing contraceptive methods. Various spermicides continued to be used for contraception in the late 19th century, e.g. cocoa-butter and quinine,
boric acid, lactic acid, chinosol, hexyl-resorcinol, ricinoleic acid, formaldehyde, etc. Foam contraceptives for insertion into the vagina were first introduced in Germany in the early 1920s, and these were thought to improve the distribution of spermicide within vagina and improve effectiveness.

**Development of hormonal contraception**

The development of an oral contraceptive started with the discovery, by John Beard in 1897, of the role of the corpus luteum in inhibiting ovulation during pregnancy. The role of the pituitary in controlling the ovarian cycle, and the subsequent discovery by Moore and Prince in 1932 of the pituitary feedback mechanism, opened up possibilities of inhibiting ovulation with hormonal therapy. In 1940, Schering released the first commercial preparation of a progestogen named Proluton C, "corpus luteum preparation for oral administration" for habitual abortion and spasmodic dysmenorrhoea, which later was also used for treatment of cystic endometrial hyperplasia and functional dysmenorrhoea [10]. Sturgis and Albright, in 1940, injected oestrogen into young women to relieve dysmenorrhoea by inhibiting ovulation. The next logical step was to discover a product, which when given by mouth, would be equally effective. Ethisterone, discovered in 1938, was found to be weakly active when orally administered. By 1956, Syntex reported that norethisterone was a powerful orally-active progestational agent which was also an effective
contraceptive. This progestogen with a small dose of oestrogen proved to be a reliable contraceptive and was rapidly labeled the “Pill” [11], [12].

Increasing knowledge of the roles of steroidal hormones in the complex processes of ovarian function, ovulation, and conception prompted numerous studies on other potential mechanisms by which these hormones could be used as contraception. These studies led to discoveries that oestrogen and/or progestogens could interfere with sperm transport, fertilization and blastocyst implantation when administered in adequate high doses following coitus. High doses could also interfere with ovarian follicle development, ovulation and corpus luteum function.

Development of Emergency Contraceptive Pill

Two ways of using contraceptive steroids as an ECP were explored initially. The first was the repeated use of an ECP following each act of unprotected intercourse [13, 14] and the second was administration of ECP only for true “emergency” situations to prevent conception after a single act of unprotected intercourse [15, 16]. The first preparation to be described for emergency contraception was high dose oestrogen [17, 18]. Van Wagenen was the first who demonstrated in experiments carried out on monkeys that oestrogens given parentally immediately after copulation reliably prevented conception [18,
Morris and Van Wagenen treated rhesus monkeys with diethylstilboestrol (1-25 mg), ethinyloestradiol (10 mg) or 2-methyl-3-ethyl-4-phenyl-4-cyclohexane carboxylic acid (ORF-3858) (10 mg) after coitus. When oestrogens were used compared to three of these synthetic oestrogens were highly effective in pregnancy prevention – there were no pregnancies reported in two years of breeding with 321 cases of positive mating when oestrogens were used compared to three years of breeding with cases of 204 positive mating and 42 pregnancies without treatment. Later, other researchers reported similar data [20].

The Canadian researcher Albert Yuzpe published a study on the use of existing oral contraceptive pills as an effective postcoital contraceptive method [21]. Referred to as the “Yuzpe regimen”, this treatment consisted of 0.1 mg ethinyloestradiol and 0.5 mg LNG, given within 72 hours of the intercourse and repeated after another 12 hours [21, 22] and was the most commonly used method of EC until recently. It was initially made available mostly by health providers in their offices or in emergency clinics for women presenting after a sexual assault. It was only in 1997 that the US Food and Drug Administration (FDA) approved six brands of oral contraceptive pills for specifically off-label prescription use as EC. One year later, the first dedicated product, Preven, received FDA approval, and in 1999 the first progestin-only ECP was approved [23]. Schering PC4 was available in the United Kingdom from 1984 onwards.
and was withdrawn in October 2001 following the successful launch of Levonelle (LNG ECP) [24].

The high-dose combined oestrogen-progestogen (Yuzpe) method produces a moderate amount of nausea and vomiting, but otherwise has a good safety record. A frequency of vomiting of 20% was reported when the “Yuzpe method” was used in comparison to 6% of cases when high dose LNG was used [25]. The World Health Organization has stated that there are no contraindications for the use of progestogen only ECP [26]. The guidelines from the Faculty of Family Planning and Reproductive Health Care of the Royal College of Obstetricians and Gynaecologists regard a history of thromboembolism as a relative contraindication and migraine at presentation, with a history of migraine with aura, an absolute contraindication to the use of Yuzpe type of ECP [27]. The use of progestogens has become more acceptable due to a lower rate of nausea and vomiting and its thromboembolic safety. There have been publications on the use of norethisterone [28], quingestanol acetate [14, 29], and D-norgestrel or levonorgestrel (LNG) [13, 30, 31]. LNG was found to have the highest progestogenic activity among the mentioned agents. In a Hungarian study, Seregely and Vero [32] reported high effectiveness and a low frequency of side effects for LNG for ECP when the single high dose of 0.75 mg was used for a single episode of unprotected sexual intercourse. It is recommended for use not more than once a week and no more than four times a month. Later
Seregely published results of a multicentre trial (8815 cycles of 1315 women, 27 253 intercourses), which confirmed high efficacy (99.9%) of Postinor (containing 0.75 mg of LNG) and low rate of side effects (withdrawal and spotting bleeding). Pregnancy occurred in 23 cases, 6 were due to the failure of the medication, and 17 to the non-compliance of the clients [33].

LNG was first licensed as an ECP in Hungary by manufacturer Gedeon-Richter in 1980 [34]. It has taken a few decades for Postinor to get recognition of being safe and effective ECP internationally [35].

LNG is a synthetic 13 β-ethyl substituted 19-nor steroid with potent progestogen activity. LNG represents the active isomer of norgestrel. The most widely currently used ECP is a progestogen-only preparation, containing LNG which has been shown to have both the highest efficacy and the lowest rate of side effects [25]. Alone or in combination with oestrogenic compounds, LNG has been used very widely for EC.

### 2.3. Types of emergency contraception

The first high-dose hormone drug used for emergency contraception was diethylstilbestrol [36]. After diethylstilbestrol, two other main forms were
developed: the combined Yuzpe regimen which uses large doses of both oestrogen and progestin taken as two doses at twelve hours intervals; and the LNG alone ECP. The LNG ECP has proven to be highly effective with limited side effects and has almost completely superceded the Yuzpe preparation.

The progestogen-only method uses LNG in a dose of 1.5 mg, either as two 0.75 mg doses 12 hours apart or as a single dose. This method has been shown to be more effective and better tolerated than Yuzpe method [25], and is available in Australia as Postinor® (Schering).

Dedicated products (all with the same LNG content) such as Postinor® (in Australia), Plan B (in US and Canada), Levonelle (in UK), NorLevo (in France) are specifically designed and marketed as emergency contraception pills. It is also possible to obtain the same dosage of LNG, and therefore the same effect, by taking a total of 25 LNG-only minipills on two occasions twelve hours apart (Microlut®, Schering or Microval®, Wyeth).

The progesterone receptor modulator drug mifepristone may be used either as an ECP or as abortifient, depending on whether it is used before or after implantation. In the USA and many other countries it is most commonly used in
200 or 600 mg doses as an abortifacent, however, it is commonly used as ECP in China. A low dose (<10 mg) is less effective than higher when it is used for ECP, but it has fewer side-effects [37]. The pregnancy rate increases by a factor of 1.6 when the dose of 10 mg is used instead of 25 mg (95% confidence interval: 1.1-2.4). In terms of the number of women needed to treat, however, using 10 mg in the place of 25 mg implies having one extra pregnancy for every 146 women requesting emergency contraception, which might be a low cost compared to the benefit of more women having access to treatment. The smallest dose of mifepristone available in the USA is 200 mg [38].

A review of studies in humans concluded that the contraceptive effects of the 10-mg dose are due to its effect on ovulation [39], but understanding of the mechanism of action remains incomplete. Mifepristone is effective in terminating established pregnancies, e.g. it is abortifacent, unlike LNG [37]. Mifepristone consists from 19-nortestosterone which has anti-progestagenic and anti-glucocorticoid effects. Mifepristone is a competitive inhibitor of progesterone receptors, which results in decreased progesterone and increased oestrogen levels [40]. Progesterone receptors are found predominantly in reproductive organs, therefore, mifepristone exerts its effect predominantly on the uterus (degeneration and shedding of endometrial lining). In addition, mifepristone increases sensitivity of myometrium to prostaglandins, which leads to contractions.
A study undertaken in Australia reported similar pregnancy rates with three single doses of mifepristone (10, 50, and 600 mg) [41]. There has been a significant amount of controversy around this study, which resulted in one of the principle investigators being investigated by the Major Crime Squad in New South Wales. The Secretary of the Federal Department of Health was taken to the Federal Court for not stopping a study that was regarded as being against the interests of the Australian population by a strong minority group that regards emergency contraceptives to be abortificents. These actions were not successful [41]. The use of mifepristone as ECP was not feasible following changes to the Therapeutic Goods Act (11 June 1996)[42], which required the signature of the Minister of Health on any import license for a drug that has the potential to be used as an abortificant. Thus, abortificant drugs were banned in Australia in 1996. In late 2005, a Private Member’s bill was introduced to the Australian Senate to lift the ban and transfer the power of approval to the Therapeutic Goods Administration. The move caused much debate in the Australian media and amongst politicians. The Bill passed the Senate on 10 February 2006, and mifepristone is now available in Australia under very specific conditions to be used for medical termination of pregnancy [43, 44].

A completely different method of EC involves insertion of a copper intrauterine device within 5 days of unprotected intercourse [45], but it is rarely used for this
purpose in Australia, although this is a fairly common indication in the UK. It has a high efficacy rate for this indication [46]. It also has the advantage of providing ongoing long-term contraception. Based on 8,400 postcoital insertions, Trussell et al estimated the failure rate of the copper IUD for emergency contraception as ≤0.1%. The copper IUD has several possible mechanisms of action as EC, including alteration of sperm motility and integrity, interference with fertilization, and prevention of implantation [47, 48], the primary ones being prevention of sperm migration and fertilization.

2.4. Clinical usage of emergency contraceptive pill

A. Efficacy and dosage of ECP

Calculation and reporting of the efficacy of ECP is a complex and controversial issue. A few studies have been carried out to estimate efficacy of ECP. The “treatment failure rate” is the percentage of women who get pregnant despite using ECP. The failure rate of ECP is 1-3%. The risk of pregnancy after a single episode of unprotected sexual intercourse is 2-4% [49], and the majority of women will not get pregnant after one episode of unprotected sexual intercourse even if they do not use ECP. Therefore, the “efficacy” of ECP, which is defined as the proportion of expected pregnancies that were prevented by ECP, is more useful measure. Kesseru and co-authors (1973) looked for the first time at the efficacy of D-norgestrel (0.4 mg) when used postcoitally and
found out that its failure rate was 3.5% [13]. The failure rate in another study [29] using 3.35 mg of D-norgestrel was 2.2%. Seregely and Vero [32] looked for the first time at the efficacy of Postinor (a commercial single dose LNG 0.75 mg, Schering, Berlin) taken for EC and found that its efficacy was 99.9% and failure rate 3.4%. Ho and Kwan [50] carried out a randomized study to compare the standard Yuzpe regimen with 0.75 mg LNG administered twice, 12 h apart, starting within 48 h after a single episode of unprotected sexual intercourse. The efficacy of LNG was similar to that of a combined oestrogen-progestin regimen with failure rates of 2.4% and 2.6%, respectively.

Recently, a randomized, double-blind clinical trial of LNG versus the Yuzpe regimen that enrolled nearly 2,000 women was reported by the World Health Organization Task Force on Postovulatory Methods for Fertility Regulation [25]. In this study, each participant received two sets of two tablets, e.g. LNG (0.75 mg, repeated 12 h later) plus placebo or the Yuzpe regimen (ethinyloestradiol 100 mcg plus LNG 0.5 mg, repeated 12 h later) plus placebo. Among 1955 women, the crude pregnancy rate was 1.1% (11/976) in the LNG group compared with 3.2% (31/979) in the Yuzpe regimen group. The crude relative risk of pregnancy for LNG compared with the Yuzpe regimen was 0.36 (95% CI 0.18-0.70). The proportion of pregnancies prevented (compared with the expected number without treatment) was 85% (74-93) with the LNG regimen and 57% (39-71) with the Yuzpe
regimen. The efficacy of both methods declined significantly with increasing time since the episode of unprotected intercourse. The pregnancy rates were 0.4%, 1.2% and 2.7% when LNG was given within the first, second and third 24 hours period since unprotected sex, respectively. In all studies, LNG was associated with a significantly lower incidence of side effects than the Yuzpe regimen [25, 50]. Therefore, currently LNG is the recommended hormonal regimen for EC.

Different doses of LNG have been tested for EC, the most common being 0.75 mg taken twice within 12 hours. A recent study has shown that the single dose 1.5 mg of LNG is as effective as a double dose of 0.75 mg taken twice 12 apart and does not cause a higher rate of side effects (41). The single dose of 1.5 mg is more convenient in use and therefore, it is the currently recommended dose of LNG for EC [6].

There is a debate in the literature on the efficacy of ECP and the mode of its calculation. It is impossible to carry out a randomized placebo-controlled study on the effectiveness of ECP and, thus, all the current attempts to calculate the efficacy of ECP were undertaken using indirect methods [49, 51-53]. Efficacy of ECP is estimated by calculation of the ratio of the number of observed pregnancies to the number of pregnancies expected [54]. The expected
number of pregnancies is estimated by multiplying the number of treated women who had unprotected sexual intercourse on each day of the menstrual cycle in relation to ovulation by external estimates of the probability of conception resulting from unprotected sexual intercourse on that day of the cycle. The expected day of ovulation is conventionally estimated as being around the 14th day before the next menses. The highest probability of conception usually occurs on the day before ovulation, although it has been shown that only a small percentage of women ovulate exactly 14 days before onset of menses [55].

There have been a few attempts to design external estimates for the probability of conception [49, 51-53]. The first study on the daily chance of conception was published in 1967 by Barrett and co-authors [51]. Their data were contributed by 241 British married couples with previously proven fertility. They were regulating their fertility by measuring the basal body temperature. The analysis was based on all data by couples who wished to conceive as well as those who were avoiding pregnancy. The authors observed 101 pregnancies in 1543 cycles. The probability of conception reported in this study was 0.13, 0.2, 0.17, 0.3, 0.14, 0.07 on day 10, 11, 12, 13, 14, 15, respectively, of the menstrual cycle where day 14 was considered an ovulation day. The problem with this calculation was that the method of determining timing of ovulation using the
basal body temperature chart was shown to have only a 30% correlation with the simultaneous ultrasonographic diagnosis of ovulation [56].

Another study widely quoted in the literature was carried out by Wilcox and co-authors [49]. This study recruited 221 North Carolina women who were planning to become pregnant. As soon as they stopped using contraception they started collecting daily urinary specimens to measure oestrogen and progesterone to estimate the day of ovulation. The ratio of oestrogen and progesterone metabolites in urine decreases abruptly with luteinization of the ovarian follicle. This measure of timing of ovulation corresponds fairly closely with the LH peak [57]. Women in this study were also asked to keep daily records of sexual intercourse. They were followed until they became pregnant or for a maximum of 6 months. In this study 146 women contributed 620 ovulatory cycles and 192 conceptions, which included 48 early pregnancy losses, only three of which were thought to be recognizable by the women. For calculating conception probability this study used the model designed by Schwartz et al. [52] This expanded model allows for the occurrence of some nonviable cycles where ovulation has not occurred. Therefore, “cycle viability”, which is an adjustment for such conditions as release of a healthy egg and adequate preparation of the endometrium for implantation, is added into calculations. The probabilities of conception calculated by Wilcox et al. (1995) were as follows – 0.10, 0.16, 0.14, 0.27, 0.31, 0.33 – on day 9, 10, 11, 12, 13,
and 14, respectively, of the menstrual cycle [49]. The algorithm used in this study to identify the ovulation day is more precise than basal body temperature and was shown to determine ovulation day in 88% of the cycles [57]. Chances of conception were clearly maximal with intercourse on days 13 and 14.

Trussell and co-authors [53] carried out a study estimating conception probabilities and the effectiveness of ECP using both British [51] and North Carolina [49] data and taking into account all conceptions and clinically recognizable ones separately. Trussell’s calculations of the conception probabilities (pooled data for recognizable conceptions) were 0.04, 0.14, 0.15, 0.28, 0.30, 0.12 and 0.04 for days 9, 10, 11, 12, 13, 14 and 15 of the menstrual cycle, respectively. These data suggested that conception chance was maximal on days 12 and 13.

Wilcox et al. [58] published new estimations of probabilities of pregnancy adjusting for post-ovulatory ageing of the human oocyte which may cause early pregnancy failure. This observational study showed that conception following intercourse on the ovulation day was accompanied by the highest chance of oocyte ageing. The calculated probabilities of successful pregnancies in this study were 0.04, 0.13, 0.08, 0.29, 0.27, 0.08, 0.01 on the cycle day 9, 10, 11, 12, 13, 14, and 15, respectively, i.e. low chance of successful conception on day 14.
There were a few other attempts to make calculation of conception probabilities more precise taking into consideration variations of ovulation day [59] as well as irregularity of menstrual cycles. Authors used the same North Carolina data. Since ECP can delay the next menses, which could lead to bias in estimating ovulation day when counting backwards from the following menses (which was a case in all previous studies), this study calculated ovulation day when counting forward from the previous menses. This could also have errors because of the variability of follicular phase length. Authors also calculated conception probabilities for each day of the cycle for women with regular and irregular menstrual cycles.

Another issue with estimating the efficacy of ECP arises because almost all studies rely on women’s report on the day of the menstrual cycle when they had unprotected sexual intercourse, which has been shown to be unreliable [60-62]. Another issue in calculating the efficacy of ECP is relying on the fact that the woman had only one episode of unprotected sexual intercourse in the cycle in which ECP was taken, which is not always the case [25]. There are a few other assumptions, which may influence the calculations including that all the users of ECP are fertile (woman as well as her partner) and that each cycle is ovulatory.
It is obvious that calculation of the ECP efficacy is not an easy exercise and requires consideration of multiple variants, e.g. precise time of the unprotected sexual intercourse during the menstrual cycle, couples fertility, timing between the unprotected sexual intercourse and the ECP intake. It seems that ECP efficacy has been grossly overestimated as the chance of conception during a particular cycle is on average low and if intercourse occurring after ovulation will not lead to pregnancy.

**B. Side effects of LNG ECP**

The most common side-effect of all forms of ECP are nausea and vomiting, and some women may experience headache, dizziness, fatigue, breast tenderness, and changes in the next menstrual period [25, 63]. Nausea and vomiting are the most common side effects, and are more common with the combined regimen (43 and 16 percent, respectively) than the LNG-only regimen (18 and 4 percent, respectively) [64]. The World Health Organisation study (1998) has also reported that onset of the menses after taking ECP might early or late by up to one week, but the duration of menses was normal of 4-7 days. The use of ECP only affects the cycle the woman is currently in, not future cycles. No significant or medically dangerous side effects have been reported during many years of ECP use.
There was initially some concern that the use of ECP might increase a woman’s risk for the development of an ectopic pregnancy, but a recent large scale review of the literature indicates that of over 33,000 women who used ECP included in the studies reviewed, only 5 ectopic pregnancies were reported, which is the same or lower than the expected rate of ectopic pregnancy in the general population [65].

In another large study the adverse events reported during the use of LNG ECP were fatigue (17 - 24%), flu syndrome (1%), abdominal pain (18%), nausea (16 - 23%), vomiting (3 - 6%), diarrhoea (5%), dizziness (11 - 18%), headache (17%), breast tenderness (11 - 16%), increased bleeding (14%) and vaginal haemorrhage (1 - 3%). These events however were similar to or much lesser in frequency than seen with the Yuzpe method. In particular, nausea and vomiting were much less frequent in LNG ECP users than the “Yuzpe method” users. Adverse effects did not result in any discontinuations in either study nor were ectopic pregnancies or congenital abnormalities reported [50].

C. Contraindications to use of LNG ECP
There are no contraindications to multiple uses of ECP. LNG ECP is only contraindicated in women with a prior allergic reaction to Postinor, known or suspected pregnancy (because it will not work, not because of teratogenic effects), or undiagnosed abnormal vaginal bleeding. Postinor is not recommended in patients with severe hepatic dysfunction. Severe malabsorption syndromes, such as Crohn's disease, might impair the efficacy of Postinor. Conditions which are considered relative contraindications include severe hypertension (BP>180+/110+), diabetes mellitus with nephropathy, retinopathy, neuropathy or vascular disease, ischaemic heart disease, stroke, or a past history of breast cancer. However, since exposure to LNG with Postinor is brief, the risks of pregnancy in all women, including those with pre-existing medical conditions, are almost certainly greater than those associated with Postinor (Schering, Berlin).

The herbal preparation of St John's Wort and enzyme-inducing drugs (e.g. anticonvulsants and rifampicin) theoretically may reduce the effectiveness of ECP and a larger dose may be required (LNG 1.5 mg initial dose and an extra 0.75 mg after 12 hours) [66, 67]. The Family Planning (2006) advises women taking a liver enzymes inducing drug to be given LNG 3 mg as a single dose.

2.5. Mechanism of action of emergency contraception pill
For conception to occur multiple factors have to be in place, e.g. folliculogenesis, ovulation, fertilization, implantation. There is long-standing debate around the definition of the beginning of pregnancy. The definition of pregnancy starting from the implantation has been adopted by the American Medical Association as well as the British Medical Association [68]. There are several theoretical ways that ECP may function to prevent pregnancy - interfering with ovarian follicular growth and function, ovulation, fertilization or implantation, migration and function of spermatozoa, which may interfere with sperm migration, function, fertilization and implantation. It may cause endometrial changes [69, 70]. LNG could work by altering any or all of these mechanisms depending on the day of the cycle at which the contraceptive is given. ECP is not an abortifacient and will not harm or cause teratogenic effects to an existing pregnancy [63, 69].

Despite the fact that a few studies have been undertaken to investigate efficacy of LNG as a postcoital contraceptive, its modes of action remains unclear. A most important question today is whether LNG ECP has any effect on post-fertilization events in a very early developing pregnancy. If LNG ECP does not work after fertilization has occurred that would change its place in contraceptive options for many people who consider that human life begins at fertilization.
Effects of ECP on human sperm transport and function

Kessuru and co-authors [13] showed that single administration of LNG ECP postcoitally decreased the number of sperm recovered from the uterine cavity 3 h after the treatment, caused pronounced alkalization of the uterine fluid beginning at 5 h after ingestion and increased the viscosity of the cervical mucus, beginning at 9 h. Effects on sperm function in vitro are dose-dependant and results vary. One study has shown dose-dependant effect of LNG on zona-binding capacity and sperm velocity, but no effect on acrosome reaction [71]. Another study reported a dose-dependant increase in acrosomal reaction when human sperm were exposed to LNG [72]. Although it is assumed that all these events could contribute to the prevention of pregnancy, it is unknown how important each change actually is during ECP use. The results reported by Kessuru and co-authors are probably of importance when LNG is used as a regular contraceptive, but unlikely to have an effect in ECP since sperm can be retrieved from the Fallopian tube within minutes after insemination [73].

Effects of ECP on ovarian follicular function

Several studies have investigated the effects of LNG ECP on ovarian function at different stages of the menstrual cycle. Landgren and co-authors examined the effects of repeated doses of LNG ECP (0.75mg) given at precise times before, during or after ovulation [74]. Administration in the early follicular phase
increased the duration of this phase of the cycle. Treatment around ovulation resulted in varying effects ranging from anovulation or deficient luteal function in some women to normal ovarian function in others. The administration of LNG ECP during the luteal phase was not followed by changes in cycle length or endometrial morphology.

In a recent study [3] which investigated the effects of short-term administration of LNG ECP on ovulation and luteal phase function in ovulating women who had undergone sterilization, results were consistent with other studies showing that preovulatory administration of LNG ECP alone or in combination with oestrogens suppresses or delays ovulation in most but not all cases. In this study ovulation was suppressed in 80% (12 of 15) of participants receiving LNG ECP in mid-follicular phase [3]. By contrast, ovulation occurred in all those women treated immediately before the LH preovulatory surge (eight women) or immediately after the LH surge (11 women), however, in these participants, deficient progesterone production with significantly shorter luteal phase length was observed. Similar results were obtained in another study and LNG given after ovulation had only minor effects on luteal function [2].

**Effects of ECP on fertilization**
Recent animal studies (in rats and Cebus monkeys) have suggested no effect of LNG ECP on post-fertilization events [4, 5]. It was shown that injection of LNG to rats before or after mating, or before implantation had no effect on fertilization or implantation, although preovulatory injections of LNG were able to inhibit ovulation and therefore prevent pregnancy [5]. Ortiz and co-authors reported that LNG can inhibit or delay ovulation in Cebus monkeys, but, once fertilization has taken place, it cannot prevent the establishment of pregnancy. These findings do not support the hypothesis that emergency contraception with LNG prevents pregnancy by interfering with post-fertilization events. There are no clear data to confirm whether oral LNG ECP interferes with post-ovulation, fertilization or implantation events in humans.

**Effects of ECP on tubal environment and function**

Mahmood and co-authors have confirmed that progesterone regulates tubal transport *in vitro* [75]. Cilia from the human Fallopian tube beat significantly slower after treatment with high doses of progesterone, an affect that could be reversed by mifepristone. The treatment with 0.75 mg of LNG twice with 12 h interval did not affect the distribution of progesterone or oestrogen receptors. The tubal effects of LNG are unlikely to contribute to its mode of action as an ECP.
Effects of LNG ECP on endometrium

One study suggested that the post-coital contraceptive effect of LNG ECP could be due to changes in the endometrium that could prevent implantation [29]. In contrast, another study has found that LNG (0.75 mg taken twice) administered 2 days post LH surge did not effect endometrial morphology or any studied markers of receptivity [2, 3].

No studies that have investigated the efficacy of LNG regimen taken for EC in relation to exact timing of ECP intake during menstrual cycle, in particular before, around or after ovulation. The above-mentioned studies on animals that had looked at an effect of LNG in EC on ovulation have suggested that LNG taken for EC may prevent pregnancy primarily by interfering with ovulation. Therefore, it has been hypothesized that LNG is effective for EC only when taken before ovulation. Further research is needed to prove this hypothesis.

If LNG does not prevent pregnancy when taken post-ovulation, women should be recommended another method of EC in a case they had ovulation. The intercourse occurring after ovulation will not lead to pregnancy, but if woman has an episode of unprotected sexual intercourse before ovulation, but took ECP after ovulation occurred, it may not work to prevent the pregnancy and another method of ECP should recommended in such cases. In addition, a
proof that LNG works only by prevention of ovulation but not by interfering with processes taking place after fertilization is very important for some catholic countries. No one has precisely evaluated the timing of ovulation by detailed hormone assays in relation to LNG EC in a large number of women around ovulation.
3. MATERIAL AND METHODS

3.1. Participants

One hundred and ten women were recruited in six Family Planning clinics in NSW (61 in Newcastle, and 16 in Chatswood, Hurstville and Penrith) and in Queensland (21 in Brisbane and 12 in Toowoomba), at the time that they presented with a request for emergency contraception. Women who agreed to participate in the study were in good health, of reproductive age (15-43 years old, mean 23.4 years), had regular periods (menstrual cycle lengths between 21 and 35 days), and reported a single act of unprotected sexual intercourse within the previous 120 hours. Women who had used hormonal contraceptives or an intrauterine device during the four weeks prior to presentation, who were pregnant, breastfeeding, or were unable to abstain from further unprotected intercourse for the remainder of their current menstrual cycle were excluded from the study.

The Ethics Committee of FPA Health gave approval for the study for all centres. All participants received a detailed information sheet, a thorough discussion of the information and signed an informed consent form.

3.2. Study Design

The primary outcome of the study was the number of pregnancies that occurred when ECP was taken before and after ovulation. Women who agreed to
participate in this study were asked to complete a questionnaire recording their reproductive and social histories as well as their knowledge about EC (Appendix 1).

All women took LNG 1.5 mg in a single dose during the course of the clinic consultation. A blood sample (8 ml of venous blood from the cubital fossa into a plain tube without anticoagulant) was taken prior to ingestion of the ECP for estimation of serum LH, E2 and progesterone levels to assist in calculating the day of the menstrual cycle. Blood samples were allowed to stand for at least 20 minutes and then were centrifuged and serum was separated and frozen at -20°C until the specimens were sent to the Department of Endocrinology, Royal Prince Alfred Hospital, Sydney, Australia to be analysed in a single batch. Women were followed up by phone call 4-6 weeks later to ascertain their menstrual and pregnancy status. All women who conceived had an ultrasound to confirm the pregnancy, but not as a part of this study.

Recruitment into the study initially began at a steady rate. However, we observed a fall in number of women presenting for ECP to Family Planning Clinics shortly after LNG ECP Postinor® became available over-the-counter in January 2003 in Australia. The study had to be discontinued soon after this because of the poor attendance of clients to the clinics for ECP. The recruitment rate was 70% of those eligible and the most common reason for refusal to participate in the study was the requirement to have venepuncture.
1.3. Hormone assays

The levels of $E_2$ and progesterone were measured by chemiluminescent immunoassay using the Immulite® 2000 analyser [Diagnostic Products Laboratories (DPC), Los Angeles CA], Reference ranges for $E_2$ were provided by DPC. They used $E_2$ values obtained in a multi-national study involving women in apparent good health (age 16-44 years), who volunteered to have daily blood samples throughout one complete ovulatory cycle. The range of intervals for $E_2$ were $<$587 pmol/L in the follicular phase, 124-468 pmol/L in the periovulatory phase, 101-905 pmol/L in the luteal phase. The analytical sensitivity was 55 pmol/L for the $E_2$ assay and 0.6 nmol/L for the progesterone assay. Reference ranges for progesterone obtained from a study by Vankrieken (2000) were $<$3.6 nmol/L in the follicular phase, 1.5-5.5 nmol/L in “midcycle”, 3.0–68 nmol/L for the early luteal phase, 19–76 nmol/L in the midluteal phase. The normal cycle serum levels for progesterone are shown in figure 1, which demonstrates the sharp rise in serum progesterone levels beginning around the day of the LH peak. The data for each hormone were orientated around the LH peak.

LH was measured by means of a microparticle enzyme immunoassay using the Abbot AxSYM® system (Abbott Chicago IL). The LH reference range was obtained from the manufacturer and was based on specimens obtained daily from 26 women with regular menstrual cycles. Normal ranges were determined
to be: 1-18 IU/L in the follicular phase, 24-35 IU/L at the mid-cycle peak, 0.4-20 IU/L in the luteal phase.

3.4. Calculation of timing of ECP administration and of unprotected intercourse in relation to ovulation

We initially pinpointed the day of the cycle according to serum progesterone levels (figure 3.1) and subsequently adjusted it according to LH and E2 levels. This calculation allowed us to pinpoint the day of the cycle within ±24 hours with reasonable accuracy. The time of probable ovulation was calculated primarily on the absolute level of progesterone, with the day of ovulation being designated as day 14. A serum level of 1-3 nmol/L was assumed to indicate day 12 or less, 2–5nmol/L as probably indicating day 13; 3–7 nmol/L as probably indicating day 14; 5–17 nmol/L as probably indicating day 15; 9–24 nmol/L as probably indicating day 16 or later. These calculations were then modified by serum LH. LH greater than 25 IU/L indicated the day of the LH peak (day 13); between 15-24 IU/L indicated the day before or the day after the LH peak depending on the serum progesterone and E2 levels. A serum E2 level of greater than 450pmol/L indicated the E2 peak on day 12. A level of E2 between 300 and 450 pmol/L indicated day 11 or day 13 (or later in the luteal phase) depending on the LH and progesterone levels. The timing of unprotected intercourse in relation to ovulation was calculated based on women’s report of the time of the intercourse.
Figure 3.1. Menstrual cycle plot for serum progesterone levels in 27 women with regular menstrual cycles sampled on a daily basis through the menstrual cycle.

We divided this 'idealised' menstrual cycle as follows: early follicular phase days 1-5, midfollicular days 6-9, late follicular days 10-12, periovulatory days 13-15, early luteal days 16-18, mid luteal days 19-25, late luteal days 26-28. The $E_2$ peak is on day 12, the LH peak on day 13 and ovulation is on day 14.

3.5. **Calculating the efficacy of the LNG ECP**

To determine the efficacy of the ECP we compared the number of observed pregnancies with the number of expected pregnancies [49, 53]. Prevented pregnancies were calculated by subtracting the ratio of expected pregnancies
to observed pregnancies from one. Expected pregnancies were calculated by multiplying the number of women having unprotected intercourse on each day of the menstrual cycle by the probability of conception on that day of the cycle, using the conception probabilities described by Wilcox [49, 53]). The fertile period of the cycle was taken to extend from five days before ovulation to the day of ovulation [49].

3.6. Statistical Analysis

Data were analysed using Excel 2003 and SPSS 11.5 (SPSS Inc, Chicago, IL). Variables that were normally distributed are presented as means and standard deviations and were analysed using the independent and paired t-test. Confidence intervals (CIs) were used where appropriate, and statistical significance was defined as $p<0.05$. 
4. RESULTS OF THE MAIN STUDY ON THE MECHANISM OF ACTION OF LEVONORGESTREL EMERGENCY CONTRACEPTIVE PILL

4.1. Demographic characteristics of participants and their reproductive history.

One hundred and ten women aged 15 to 43 (mean 21, SD 7.6) were enrolled in this study but eleven women were excluded due to insufficient blood samples for complete hormonal analysis. Therefore, 99 women were investigated.

Sixty women had not been pregnant previously, 14 had one pregnancy, 6 had two pregnancies, 6 had more than three pregnancies and 2 women did not report their reproductive history. Forty-nine women had used ECP previously. Twenty women had used the ECP once, 11 twice, seven - three times, four - four times, and another eight women used it five or more times. One woman reported becoming pregnant after previous use of the Yuzpe method of EC.

4.2. Results of the determination of timing of ECP administration and of unprotected intercourse in relation to ovulation

Three women became pregnant during this study despite taking the ECP (3%). All three women who became pregnant took the ECP in the early luteal
phase based on hormonal estimations. Hormonal levels, time of sexual intercourse and day of taking the ECP in these three cases are presented in Table 4.1. For subject number 1 endocrine data suggested that unprotected intercourse may have occurred 24 hours around ovulation time (day 0) and ECP was taken 33 hours after unprotected intercourse, which was just around ovulation or after ovulation. Subject number 2 may have had unprotected intercourse 24 hours before or after ovulation, and ECP was taken 66 hours after unprotected intercourse, thus about 24-48 hours after ovulation. For subject number 3 endocrine data suggested that unprotected intercourse may have occurred 12 to 24 hours after ovulation.

Table 4.1. Timing of sexual intercourse and taking the ECP for three women who became pregnant, based on serum hormone levels at the time of ECP administration.

<table>
<thead>
<tr>
<th></th>
<th>E₂</th>
<th>P₄</th>
<th>LH</th>
<th>Hrs between IC and ECP</th>
<th>Day of sexual intercourse</th>
<th>Day of ECP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>214</td>
<td>11.5</td>
<td>10.6</td>
<td>33</td>
<td>0±1</td>
<td>+2±1</td>
</tr>
<tr>
<td>2</td>
<td>154</td>
<td>13.1</td>
<td>12.7</td>
<td>66</td>
<td>-1±1</td>
<td>+2±1</td>
</tr>
<tr>
<td>3</td>
<td>181</td>
<td>13.2</td>
<td>8.4</td>
<td>20</td>
<td>0±1</td>
<td>+2±1</td>
</tr>
</tbody>
</table>
Distribution of timing of unprotected intercourse and taking ECP based on hormonal levels during different stages of the menstrual cycle in 99 women enrolled in the study is shown in Table 4.2.

From the data in Table 4.2 it is clear that pregnancies did not occur when unprotected intercourse occurred on day -2 or earlier and the ECP was taken before day 0, whereas all 3 pregnancies occurred when intercourse took place around day −1 to 0 and the ECP was taken on day +2. Data from Wilcox et al (17,18) suggest that four or five clinical pregnancies would have been expected among the group of 34 women who had intercourse on days −5 to −2 (and took the ECP before or around ovulation), when none occurred. Among the 17 women who had intercourse around days −1 to 0, (and took the ECP on day +2) three or four pregnancies would have been expected, and three were observed.
Table 4.2. Timing of unprotected sexual intercourse and taking ECP in 99 women according to hormonally-based estimations.

<table>
<thead>
<tr>
<th>Timing of sexual intercourse</th>
<th>Early follicular</th>
<th>Mid follicular</th>
<th>Late follicular</th>
<th>Peri-ovulatory</th>
<th>Early luteal</th>
<th>Mid luteal</th>
<th>Late luteal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing of ECP</td>
<td>3</td>
<td>16</td>
<td>22</td>
<td>30</td>
<td>9</td>
<td>19</td>
<td>0</td>
</tr>
</tbody>
</table>

Forty-five women had intercourse on days -5 to -1 and eleven of these took the ECP around or after ovulation (days 0 - 2) (Figure 4.1). Only one of these women who had intercourse on day -1 and took the ECP on day +2 became pregnant.
Figure 4.2. Days of unprotected intercourse and day of taking emergency contraception calculated in relation to day of ovulation (day 0) in 99 women.

Figure legend
- The day of taking emergency contraception calculated according to serum levels of progesterone, LH and oestradiol as described earlier in the chapter on material and methods.
- Blue markers indicate day of the unprotected intercourse, the pink markers indicate the day of the ECP intake in women who did not conceive
- Black markers indicate the day of unprotected intercourse and the red markers indicate the day of the ECP intake in women who conceived
4.3. **Results of calculations of the efficacy of ECP.**

Table 1 shows the distribution of women having unprotected intercourse on different days of the fertile period (between days −5 and 0) compared with the number of clinical pregnancies. Fifty-one women had the index episode of unprotected intercourse on days -5 to 0. According to Wilcox et al data [49] we could have expected 7 to 8 clinical pregnancies in our study and we observed three pregnancies. Thus, the failure rate of the ECP was 3.0% and its efficacy in this study was found to be 60.5% based on Wilcox's calculations of pregnancy probability (17,18). Twenty-three women had their index episode of unprotected intercourse in the early to mid-follicular phase prior to day -5, and 25 had intercourse in the luteal phase.

From the data in Table 4.1 it is clear that pregnancies did not occur when unprotected intercourse occurred on day -2 or earlier and the ECP was taken before day 0, whereas all 3 pregnancies occurred when intercourse took place around day −1 to 0 and the ECP was taken on day +2. Data from Wilcox et al (17,18) suggest that four or five clinical pregnancies would have been expected among the group of 34 women who had intercourse on days −5 to −2 (and took the ECP before or around ovulation), when none occurred. Among the 17 women who had intercourse around days −1 to 0, (and took the ECP on day +2) three or four pregnancies would have been expected,
and three were observed. Hormonal levels, time of sexual intercourse and day of taking the ECP in these three cases are presented in Table 4.2. For subject number 3 endocrine data suggested that unprotected intercourse might have occurred 12 to 24 hours after ovulation. We have taken this to be day 0.
Table 4.3. Distribution of women having unprotected intercourse in the fertile period of the menstrual cycle based on endocrine data and probability of clinical pregnancy using Wilcoxon calculations (Wilcoxon et al. 1995; 1998).

<table>
<thead>
<tr>
<th>Cycle day of intercourse (day 0 = day of ovulation)</th>
<th>Probability of clinical pregnancy % – based on data from Wilcoxon et al (1995; 1998) [see Table 1 of reference 18]</th>
<th>Number of women who had sexual intercourse on each cycle day (based on endocrine data)</th>
<th>Expected number of clinical pregnancies based on endocrine data and Wilcoxon calculations (1995; 1998)</th>
<th>Observed pregnancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>-5</td>
<td>4</td>
<td>7</td>
<td>0.28</td>
<td>0</td>
</tr>
<tr>
<td>-4</td>
<td>13</td>
<td>9</td>
<td>1.17</td>
<td>0</td>
</tr>
<tr>
<td>-3</td>
<td>8</td>
<td>12</td>
<td>0.96</td>
<td>4.15</td>
</tr>
<tr>
<td>-2</td>
<td>29</td>
<td>6</td>
<td>1.74</td>
<td>0</td>
</tr>
<tr>
<td>-1</td>
<td>27</td>
<td>11</td>
<td>2.97</td>
<td>1</td>
</tr>
<tr>
<td>0</td>
<td>8</td>
<td>6</td>
<td>0.48</td>
<td>3.45</td>
</tr>
<tr>
<td>TOTAL</td>
<td>51</td>
<td></td>
<td>7.60</td>
<td>3</td>
</tr>
</tbody>
</table>
4.4. **Time of taking ECP in the menstrual cycle based on women's reports and hormonal studies.**

There was substantial discord between the determination of stages of cycle from endocrine data compared with data from the woman’s self report (Figure 3). Of the 41 women, who on endocrine data were in the follicular phase of the menstrual cycle, only 16 (39%) were correct in their personal estimation, seven of these (17%) thought they were in the periovulatory phase, and 16 (39%) thought they were already in the luteal phase. Two of these women were unable to identify the stage of their cycle at the time of consultation.

Only seven women out of thirty (23.3%), who were in the periovulatory phase of the menstrual cycle according to endocrine data were correct in their own estimation of this phase. Four (13%) thought they were in the follicular phase, 16 (53%) thought they were in the luteal phase and three could not remember when their last menstrual period was (Figure 4.2).

Twenty-eight women were in the luteal phase of the cycle at the time of taking the ECP, and the majority of them [19 (68%)] reported correctly that they thought they were in this phase of the cycle: five (18%) thought they were in the periovulatory phase, two (7%) in the follicular phase and two were unable to remember the day of their cycle.
Overall, twenty-one women out of the 99 (21%) were unsure of the actual date of their last menstrual period.

Figure 4.23. Comparison between stage of cycle at time of taking ECP based on endocrine data or women’s self report.

The average time between sexual intercourse and taking the ECP was 35 hours (SD 18.1, range 7 - 95 hours). Thirty-three women (34.3%) took the ECP within 24 hours of unprotected intercourse, 42 (42.4%) within 25 to 48 hours, 23 (23.2%) within 49 to 72 hours and one woman took the ECP 95 hours after unprotected intercourse.
The failure rate of the ECP was 3.03%. The efficacy of the ECP in our study was found to be 72% based on Wilcox’s calculations of pregnancy probability [49]. Table III shows the distribution of women having unprotected intercourse on different days of the menstrual cycle during the fertile period (between day -4 and day +1 of the cycle) compared with the number of conceptions. According to the Wilcox calculations [49] we would have expected 10.2 women to become pregnant in our study. We observed three pregnancies. If the ovulation day was determined on women’s self report, the efficacy rate of the ECP was 53% based on Wilcox. Among nineteen women who were in the fertile period of their cycle and took ECP after ovulation (on day 0 -+2) we would have expected five pregnancies according to Wilcox calculations. Therefore, two out of five conceptions after ovulation occurred were prevented.

From the data in Table III it is clear that pregnancies did not occur in this study when unprotected intercourse occurred on day -2 or earlier (as the ECP was taken before ovulation), whereas the 3 pregnancies all occurred when intercourse took place on day -1 – 0 and the ECP was taken on day +2. These data are supportive of the concept that the LNG ECP has little or no effect on post-ovulation events.
5. DISCUSSION on the mechanism of action of levonorgestrel emergency contraception

The main finding of this study was the fact that LNG ECP is not effective after ovulation has occurred. All three women in the study became pregnant when they had unprotected intercourse around or before ovulation and took ECP after ovulation.

Since the introduction of ECP there have been multiple hypotheses on the mechanism of action of ECP, e.g. interference with sperm migration [13, 71-73], with ovulation [2, 3, 74], with implantation [29] and there have been several small studies in support of these theories. Our small study has shown that all three women who conceived despite taking ECP were at the same stage of menstrual cycle (day 13-14) when they had unprotected intercourse and their hormonal levels were very similar at the time they took ECP (day 16 of an ideal cycle; ovulation +2 days). In contrast, women who had unprotected intercourse and took ECP earlier in the cycle (before ovulation) did not become pregnant. This finding has not been reported in human studies previously. This finding is in agreement with animal studies showing that LNG ECP does not interfere with post-fertilisation events [4, 76]. Durand et al [3] showed that LNG, given post-coitally, has an ovulatory effect and, therefore contraceptive effect, if administered prior to the LH surge, but not after it. This study investigated effects of short-term administration of LNG on ovulation and luteal phase.
function in 45 women with tubal ligation in two consecutive cycles. Women were given 0.75 mg of LNG 12 hours apart. The first group received LNG on a day 10 of the menstrual cycle, the second group – immediately after positive LH detection in urine, the third group - 48 hours after a positive detection of urinary LH, and the fourth group – in the late follicular phase. Participants had transvaginal ultrasound performed and serum LH level checked from the detection of urinary LH until ovulation, serum oestradiol and progesterone were measured during the complete luteal phase. Participants also had endometrial biopsy on day 9 of the cycle. Eighty percent of women in the first group were anovulatory, the remaining three participants showed a significant shortness of the luteal phase. There were no significant difference in either cycle length or in hormonal levels in women in the 2\textsuperscript{nd} and the 3\textsuperscript{rd} group. Women in the fourth group had normal cycle length with significantly lower progesterone levels. The authors of this study concluded that the interference of LNG with the mechanisms initiating the LH surge depends on the stage of follicle development. Preovulatory administration of LNG resulted in anovulation. Peri- and post-ovulatory administration of LNG did not impair corpus luteum function or endometrial morphology. Other studies of the Yuzpe regimen for ECP also found that this method of contraception is unlikely to prevent pregnancy if given post-fertilization [77].

Confirmation of this important finding in larger studies would change the recommendation for use of ECP. The failure rate of LNG ECP could be
decreased if it is not used post-ovulation and other more appropriate methods of ECP are advised to clients. However, the estimation or prediction of the day of the ovulation is extremely difficult even during an “ideal” menstrual cycle. There are six days in the average menstrual cycle ("fertile period") when intercourse can result in pregnancy [78]. Conception is most likely to occur between day 11 and day 15 of the idealized 28 day cycle. Probability of conception is close to zero if intercourse occurs after day 15 of the cycle where ovulation occurs on day 14. Therefore, it is only a small number of pregnancies that won’t be prevented by LNG ECP. Although Wilcox and co-authors have pointed that only 30% of women are in the “fertile window” of the cycle between days 10 and 17 of the idealized cycle by timing the ovulation on the ratio of urinary metabolites of oestrogen and progesterone. In their study, most women reached their fertile window earlier and others much later. The author suggests that the timing of fertility window can be highly unpredictable [78].

A problem with efficacy studies of EC is pinpointing the exact time relationship of unprotected intercourse and ECP ingestion to the occurrence of ovulation. Timing is usually based on data reported by the women and calculations done by the investigator using uncertain assumptions, which have been shown in this and other studies to be quite unreliable. Stirling and Glasier reported that more than 30% of women had biochemical findings (urinary estrone/creatinine and pregnandiol/creatinine ratios) that were incompatible with their cycle day as estimated by a calendar. Even among women who were “very sure” about the
day of their cycle, 15% had inconsistent hormonal levels; among those who were “fairly sure” (±1 day), 27% had inconsistent results, and among those who were “quite sure” (±1-3 days), 42% had inconsistent results [61]. In this study we were able to pinpoint the day within or after the fertile period in which the ECP was taken to within 24 hours with an estimated 80% accuracy, based on individual endocrine data. Accuracy could have been improved had we been able to take repeated blood samples over several days and perform ultrasound examinations of the ovary at the time that blood was taken. Unfortunately this was logistically impossible. Both endocrine and ultrasound examinations are costly which will make it expensive and difficult to conduct such a study with sufficient numbers to provide adequate power, as the overall pregnancy rate in women who use EC is low.

There have been several attempts to design external estimates for the probability of conception in natural cycles [49, 51-53, 57-59], but most of these reports have relied on women’s self report of cycle day and day of intercourse, sometimes supplemented by basal body temperature or urinary hormone data.

Wilcox and colleagues [49] determined the probability of conception based on endocrine data to estimate the day of ovulation from 221 North Carolina women who provided daily urine samples for measurement of urinary oestrogen and progesterone metabolites from the time they stopped contraception until they became pregnant or had provided 6 months data. As the urinary ratio of
Oestrogen to progesterone metabolites decreases abruptly with luteinisation of the ovarian follicle, this measure of ovulation corresponds approximately with the LH peak [57].

We used endocrine data from the measurement of three hormones, which change markedly in serum in the peri-ovulatory period to predict the day on which women ovulated and took the ECP. This appears to be a more precise method (to at least 80% accuracy) of estimating the day within or after the fertile period than methods used in some studies such as basal body temperature or urinary LH. A recent study has shown that urinary LH on its own may be unreliable for determining the day of ovulation [3].

The serum level of progesterone (Figure 1) was used as the initial determinant and serum LH and E2 levels as additional determinants of the more precise time in the cycle when women took the ECP. We initially used figure 1 to pinpoint the day before, the day of or after ovulation for individual participants according to the progesterone level. The data in this graph were generated in a multinational study involving women in apparent good health [79], but these data have not been specifically validated for Australian women.

The participants in our study had similar characteristics to those enrolled in the above-mentioned study, although it is unknown if other important factors such as weight, smoking habits, and parity were also similar. The patterns of
IMMULITE data are similar but not identical to data obtained by other authors on progesterone, LH, and E₂ profiles during the normal menstrual cycle [80, 81].

We found obvious discrepancies between hormonal findings and the stage of the menstrual cycle reported by women. Self-report of cycle phase coincided with hormonal parameters only in 43.4% of women. Stirling and Glasier [61] found that hormonal results in 30% of women in their study were incompatible with the cycle day estimated by calendar, and were most likely to be inconsistent in those women presenting in the luteal phase (when their last menstrual period was more distant in their memory). In contrast, we found that endocrine data were more consistent with self-report by women in the luteal phase (67.9%) and least consistent in the periovulatory phase (23.3%). Our findings confirm that it is unreliable to base the estimation of cycle phase on women’s self report. Hormonal confirmation is required.

The “pregnancy rate” in this study was 3.0%, which is similar to other studies on the efficacy of ECP [6, 25]. All three women who became pregnant had very similar endocrine data and took the ECP around two days after ovulation (ovulation = day 0) and had unprotected intercourse between days -1 and 0. The expected number of clinical pregnancies in our study was 7 to 8 based on Wilcox probability of clinical pregnancy [49, 58]. From the data in Table 2 it is clear that pregnancies did not occur when unprotected intercourse occurred on day -2 or earlier, and when ECP was then taken around or before ovulation.
Four or five clinical pregnancies could have been expected in this group of women, but did not occur.

Our findings should certainly be confirmed in a larger study. The current study had to be discontinued due to difficulties with recruitment once LNG ECP became available over-the-counter in Australia and number of clients presenting to the Family Planning Clinics for ECP had dropped.
6. Changes in knowledge and attitudes towards use of emergency contraception in abortion seekers as emergency contraception became widely available in Australia

6.1 Literature review

Approximately 46 million abortions are performed yearly, of which 26 million are legal and the rest are illegal. Some countries, such as Belgium (11 per 100 known pregnancies) and the Netherlands (11 per 100 known pregnancies), have a low rate of induced abortion, while others like Russia (63 per 100 known pregnancies) and Vietnam (44 per 100 known pregnancies) have a comparatively high rate. It is estimated that 80,000 induced abortions are performed annually in Australia. The world ratio is 26 induced abortions per 100 known pregnancies [82]. These numbers are problematic, as unplanned pregnancy is associated with both high maternal morbidity and economic costs [83-85]. For example, in Ghana, where the HIV rates are very high, women are more likely to die from unsafe abortions than from AIDS [84].

Unplanned pregnancies occur in the small percentage of women who don’t use contraception, and in women for whom contraception fails. Unfortunately, contraception is neither universally used nor fool-proof. In a study from the USA, of all women who experience unplanned pregnancy, more than half were using contraception at the time of conception [86]. Fortunately, unplanned pregnancies are theoretically preventable, and increasing use of effective
contraception has led to an overall decline of unplanned pregnancies since 1987 in the USA [86]. Health experts estimated that widespread use of emergency contraception could prevent as many as a further 1.7 million unplanned pregnancies each year in the USA [87]. Another report suggests that almost a million abortions could be prevented in the US annually if women used EC every time they needed it [88]. Unfortunately, availability of the ECP has not been shown to decrease abortion rates [89]. In France, Sweden, and the UK, where ECP has been available for more than a decade – the abortion rate was stable or higher during that time period [85, 90].

A Scottish study concluded that distribution of free advance supplies of ECP to a large number of women did not lower abortion rates [89]. Several studies have shown that having a supply of ECP at home does increase its use by two to threefold, however, it did not have any remarkable effect on the rates of unplanned pregnancy and abortion [89, 91-93]. According to EC expert Dr. Anna Glasier, EC is “better than nothing” and “worth the fuss… if you are a woman who has had unprotected sex, “because it will work in some women some of the time”, but it is not a useful public health measure. She stated that “if you are looking for an intervention that will reduce abortion rates, emergency contraception may not be the solution, and perhaps you should concentrate most on encouraging people to use contraception before or during sex”. A randomised controlled trial of 2000 women in China compared women with advance access to EC to women without access, and noted that the
pregnancy rate was the same between the two groups. The study observed that “providing EC in advance increases use, but there is no direct evidence that it reduces unintended pregnancy” and concluded that EC may not lower abortion rates [91].

For centuries, the progress in development of contraceptive methods has been far behind in comparison to the advances in other aspects of scientific and industrial developments due to political and religious influences in this area.

Thus, until 1959, the National Institute of Health was forbidden to support research connected with contraception. In the World Health Organization, hostility from the Vatican State prohibited any response to those nations seeking help with family planning programmes [94]. Only private institutions such as Scaife, Ford, and Rockefeller Foundations continued the research in this field.

The results of a clinical trial of what were to become contraceptive pills were published in 1957 [95] and showed convincing effectiveness, and in 1960, the Searle Company marketed the first contraceptive Pill. In 1961, a study of almost 10 000 Pill users and users of barrier methods of contraception was launched [95].
The first suspicion that oral contraceptives had serious and possibly fatal side-effects became available only when data on several tens of thousands of users became available. Extensive retrospective and prospective studies were then initiated. The Pill was first marketed in 1957 for treatment of menstrual disorders, and approved by the U.S. Food and Drug Administration in 1960. The original approval was given on a series of 897 women. The issue of long-term safety was taken into consideration during the approval process, which could not have happened in modern time. The current regulations are so strict that it might have taken a few more decades for pill to be approved. On the other hand, if oral contraceptive development would have taken a place in 1930s as it was possible scientifically, they would have become available without the necessity for a medical prescription, ushering in an entirely different era of contraceptive availability.

As I mentioned earlier, development of emergency contraception became possible after development of the oral contraceptive pill. Despite the LNG ECP Postinor being available in Hungary and several other countries from 1980s, it took several decades for the rest of the World to be convinced of the efficacy and safety of this preparation. In addition, despite ECP being “available”, there was very little awareness about this preparation among medical practitioners and users in most countries until 1990s or even later.
In 1995, the Rockefeller Foundation convened a meeting to discuss emergency contraception. After the meeting, a group of seven international organizations formed The International Consortium for Emergency Contraception (ICEC) to promote EC as a part of mainstream reproductive health care provision. The seven founding member organizations were the Concept Foundation, the International Planned Parenthood Federation (IPPF), the Pacific Institute for Women’s Health, the World Health Organization, the Population Council, Population International, and the Program for Appropriate Technology in Health.

The Concept Foundation is the distribution part of ICEC. Its funding for the development of Postinor-2 came from the Rockefeller Foundation and the David and Lucile Packard Foundation, as well as the other ICEC organizations. The Consortium helped promote the availability of EC by manufacturing EC product. The ICEC worked with Hungarian pharmaceutical company Gideon Richter to repackage its contraceptive Postinor as an emergency contraceptive, called Postinor-2, and distributed it mainly in developing countries. ICEC facilitates product registration by encouraging interest in EC products through meetings with public-sector agencies and non-governmental organizations and by helping organizations applying for EC registration through the country-specific approval process. ICEC negotiated a public-sector price of ECP [95].

Emergency contraception is effective in preventing up to 84% of unwanted pregnancies in ideal circumstances [96]. The access to emergency
contraception has been rapidly improving in the last few years with the regimen being available over the counter in many countries [97, 98]. LNG ECP is available in 101 countries, and is available without prescription in 33 of them.

Easier access to a dedicated emergency contraceptive pill should contribute to more timely use following unprotected intercourse [83] and assist in reducing the number of unplanned pregnancies and pregnancy terminations. Most experts feel that the prescription-only status of ECP is medically unjustified and leads to difficulties of access. ECP are very effective and time-sensitive, and wasting time for the prescription to be obtained and filled leads to decrease in its efficacy. Women who are seeking ECP, must locate a health provider, obtain a prescription, fill it at a pharmacy, and take pills within 72 hours. This process may greatly delay the treatment especially taking into account the fact that the majority of women will be seeking the ECP after hours and on weekends. The major argument against over-the-counter provision is the loss of opportunity for evaluation and counseling by a health care provider which may lead to an increased risk of sexually transmitted infections and fall in use of regular contraception. Between 1999 and 2004 in Sweden, the use of ECP by female university students more than doubled, and at the same time there was a trend towards more risky sexual behavior with more partners, more unprotected first-date intercourse, and more unprotected self-reported sexually transmitted infections [99]. The rate of sexually transmitted infections has increased in Sweden since ECP has been available over the counter. However,
during this time there was a decline in sexual education, economic growths, and increases in drug use and school non-attendance which might have also played role [100]. At least one study has found that availability of ECP does not increase the incidence of unprotected sex [101]. It has also been shown that teenagers are not more likely to engage in unprotected sex than young adults when both have advance access to ECP. However, other studies have shown that most women are able to use emergency contraception appropriately without formal evaluation and counseling and do not abandon the use of regular contraception [102].

The most effective and easy to use method, oral levonorgestrel (Postinor) for emergency contraception [6] became available in Australia on prescription in 2002 and over-the-counter in January 2004. It was anticipated that easy access to an ECP would increase its use and therefore decrease the rate of unintended pregnancies and abortions [103]. No large studies have compared patterns of use of EC before and after it become available over the counter in Australia although this has recently been done in the UK [97]. Meanwhile considering improved ECP access, we have to remember that in many countries only a small minority of women yet realize that this product exists, e.g. only 6% of women who would need ECP have ever used it in 2003 in comparison to 1% in 1997 in a study from the US [104].
6.2. Material and Methods

Women attending for abortion at 3 clinics belonging to Australian Birth Control, two in inner metropolitan Sydney and one in an outer suburb with a lower socio-economic population, were invited to participate by completing a self-administered questionnaire during their clinic visit. A letter explaining the purpose of the survey, its confidential nature, a consent form and an envelope for inserting the completed form accompanied questionnaire. Women placed the envelope containing the unidentified completed questionnaires in a box located in the clinic waiting room. Women who declined to answer were asked to place the unanswered questionnaire in the box.

A previously validated survey provided 15 items for the questionnaire [105]. Women were asked whether they had heard about EC, whether they had sufficient information, if they had taken it before, whether they had tried to get the ECP and if they had any difficulties in obtaining it. They were also asked about worries and concerns regarding use of the ECP. Demographic data including educational level achieved and outcome of any previous pregnancies we also collected (Appendix 2).

The questionnaires were administered at each site before and 12 months after release on prescription of a dedicated ECP pack, Postinor (group 1 and 2, respectively) as well as 12 months after the ECP pack became available over
the counter in Australia (group 3). Two clinics where this study was undertaken were situated in Camperdown and Randwick, in the more central area in Sydney, and the third clinic was situated in Kingswood, an area of lower socio-economic class in compare than the other two.

Data were analyzed by means of SPSS 13.0. Where groups were compared on categorical data, chi-square analyses were employed. Comparisons of continuous data were made using one-way analysis of variance (ANOVA) for three groups and independent samples t test for two groups. Distributions of all variables were checked and transformation was conducted where data were skewed.

Approval for the study was obtained from the Ethics Committee of FPA Health

6.3. Results

A total of 719 questionnaires were returned (208 in group 1 – prior to a dedicated ECP pack release in Australia, 308 in group 2 - 12 months after an ECP pack became available in Australia and 203 in group 3 - 12 months after an ECP pack was available over-the-counter).
208 questionnaires from women in group 1 were returned from the following locations - 165 (79.3%) from the clinic Kingswood, 32 (15.4%) from the clinic Camperdown and 11 (5.3%) from clinic Randwick.

308 questionnaires from women in group 2 were returned from the following locations – 126 (40.9%) from Kingswood, 79 (25.6%) from Camperdown and 103 (33.4%) from Randwick.

202 questionnaires from women in group 3 were returned from the following locations – 92 (45.5%) from Kingswood, 94 (46.6%) from Camperdown and only 16 (7.9%) from Randwick.

**Age of participants**

Mean (±SD) ages of participants (years) were in group 1 - 25±7, group 2 - 28±7, and group 3 - 27±7. Ages ranged from 13 to 45 years. Age was significantly skewed, which was successfully rectified by applying a square root transformation. The three groups differed significantly in age (p=0.001) with the first group being younger than the other two.

**Place of residence**
Most women attended a clinic within the geographical area in which they resided (96%, n = 647/675). There were no systematic differences between the groups in the proportion of women who were not from within the Area Health Service of the clinic where they were attending (5% in group, 4% in group 2, 3% in group 3, NS).

Reproductive history

Forty per cent of women in group 1, 48% of women in group 2, and 52% of women in group 3 had one or more previous terminations of pregnancy (p=0.049). Reproductive history of responders is presented in Tables 6.1 to 6.4.

Table 6.1. Number of pregnancies, abortions, and miscarriages in women who presented for TOP before (group1), 12 months after a release of the ECP pack (group 2), and 12 months after it being available over the counter (group 3).

<table>
<thead>
<tr>
<th></th>
<th>Group 1 N=208</th>
<th></th>
<th>Group 2 N=308</th>
<th></th>
<th>Group 3 N=202</th>
<th></th>
<th>P value or NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous pregnancies</td>
<td>128 No 61%</td>
<td></td>
<td>209 No 68%</td>
<td></td>
<td>140 No 69%</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Previous abortions</td>
<td>79 No 38%</td>
<td></td>
<td>148 No 48%</td>
<td></td>
<td>99 No 49%</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Previous miscarriages</td>
<td>40 No 19%</td>
<td></td>
<td>65 No 21%</td>
<td></td>
<td>31 No 15%</td>
<td></td>
<td>0.01</td>
</tr>
</tbody>
</table>
Table 6.2. Number and percent of previous pregnancies, reported by respondents.

<table>
<thead>
<tr>
<th>Number of previous pregnancies</th>
<th>Group 1 (n=208)</th>
<th>Group 2 (n=308)</th>
<th>Group 3 (n=202)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>0</td>
<td>71</td>
<td>34.1</td>
<td>98</td>
</tr>
<tr>
<td>1</td>
<td>43</td>
<td>20.7</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>9.6</td>
<td>54</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>11.5</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>7.2</td>
<td>29</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>4.8</td>
<td>19</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>3.4</td>
<td>11</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>2.4</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>0.5</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>did not report</td>
<td>9</td>
<td>4.3</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 6.3. Number and percent of miscarriages reported by respondents.

| Number of previous miscarriages | Group 1 (n=208) | | | Group 2 (n=308) | | | Group 3 (n=202) | | |
|---|---|---|---|---|---|---|---|---|
| No. | % | No. | % | No. | % |
| 0 | 159 | 76.4 | 242 | 78.6 | 161 | 0.8 |
| 1 | 32 | 15.3 | 55 | 17.9 | 23 | 11.4 |
| 2 | 5 | 2.4 | 5 | 1.6 | 5 | 2.5 |
| 3 | 1 | 0.5 | 4 | 1.3 | 2 | 1 |
| 4 | 0 | 0 | 0 | 0 | 1 | 0.5 |
| 5 | 1 | 0.5 | 1 | 0.3 | 0 | 0 |
| 6 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7 | 0 | 0 | 0 | 0 | 0 | 0 |
| 8 | 1 | 0.5 | 0 | 0 | 0 | 0 |
| Did not report | 9 | 4.3 | 1 | 0.3 | 11 | 5.4 |
Table 6.4. Number and percent of abortions reported by respondents.

<table>
<thead>
<tr>
<th>Number of previous abortions</th>
<th>Group 1 (n=208)</th>
<th>Group 2 (n=308)</th>
<th>Group 3 (n=202)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>0</td>
<td>120</td>
<td>57.7</td>
<td>159</td>
</tr>
<tr>
<td>1</td>
<td>50</td>
<td>24.1</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>9.1</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>2.4</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>1.4</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>did not report</td>
<td>9</td>
<td>4.3</td>
<td>1</td>
</tr>
</tbody>
</table>

*Level of education*

The majority of women stated that they had completed high or secondary school, e.g. 53%; (n = 106/199) in group 1, 39% (121/307) women in group 2,
42% (81/192) in group 3. A trade or TAFE qualification had 23% (46/199) of women in group 1, 23% (72/307) of women in group 2, and 25% (48/192) in group 3. A university or college degree had 21% (42/199) of women in group 1 and 35% (108/307) of women in group 2, and 27% (52/192) women in group 3. Five women (2.4%) in group 1, six women (2.7%) in group 2, and 11 (5.4%) women in group 3 indicated that they had no school qualification. Eight women in group 1, one woman in the group 2, and 11 women in group 3 did not indicate their educational level. The distribution of educational achievement within the three groups was statistically significantly different, with women in group 2 having achieved a higher level of education ($\chi^2 = 19.93$, df = 6, p < 0.005) (Table 6.5).

Table 6.5. Educational level of responders who presented for TOP before (group1), 12 months after a release of the ECP pack (group 2), and 12 months after it being available over the counter (group 3)

<table>
<thead>
<tr>
<th></th>
<th>Group 1 N=208</th>
<th>Group 2 N=308</th>
<th>Group 3 N=202</th>
</tr>
</thead>
<tbody>
<tr>
<td>No school</td>
<td>5</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>%</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>High or secondary school</td>
<td>106</td>
<td>121</td>
<td>81</td>
</tr>
<tr>
<td>%</td>
<td>51</td>
<td>39</td>
<td>40</td>
</tr>
<tr>
<td>A trade or TAFE qualification</td>
<td>46</td>
<td>72</td>
<td>48</td>
</tr>
<tr>
<td>%</td>
<td>22</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>University or college degree</td>
<td>42</td>
<td>108</td>
<td>52</td>
</tr>
<tr>
<td>%</td>
<td>20</td>
<td>35</td>
<td>26</td>
</tr>
<tr>
<td>Did not respond</td>
<td>8</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>%</td>
<td>4</td>
<td>0.3</td>
<td>5</td>
</tr>
</tbody>
</table>

* non-responders were excluded from analysis

$\chi^2=19.93$, df=6, p=0.003
Knowledge on ECP and level of education

There was a statistically significant trend towards increased use of the ECP in women of a higher educational level ($\chi^2 = 12.7$, df=2, p=0.002) (Table 6.6). On the other hand, there was no significant difference in number of women of different educational level who had heard about ECP ($\chi^2 = 1.35$, df=2, p=0.51), who considered that they had sufficient information about the ECP ($\chi^2 = 0.82$, df=2, p=0.664), who had any worries about taking ECP ($\chi^2 = 3.46$, df=2, p=0.177), or who took ECP to prevent current pregnancy ($\chi^2 = 0.48$, df=2, p=0.787), who had difficulties obtaining ECP ($\chi^2 = 3.32$, df=2, p=0.190).
Table 6.6. Knowledge about ECP according to educational level of responders.

<table>
<thead>
<tr>
<th></th>
<th>No school</th>
<th>High school</th>
<th>TAFE</th>
<th>Uni</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>22</td>
<td>308</td>
<td>166</td>
<td>202</td>
<td></td>
</tr>
<tr>
<td>Heard about ECP?</td>
<td>77%</td>
<td>90%</td>
<td>91%</td>
<td>87%</td>
<td>NS</td>
</tr>
<tr>
<td>Ever taken ECP?</td>
<td>18%</td>
<td>38%</td>
<td>46%</td>
<td>52%</td>
<td>p = 0.001</td>
</tr>
<tr>
<td>Took to prevent this pregnancy?</td>
<td>0%</td>
<td>10%</td>
<td>8%</td>
<td>10%</td>
<td>NS</td>
</tr>
<tr>
<td>Couldn’t get ECP?</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
<td>8%</td>
<td>NS</td>
</tr>
<tr>
<td>Do you have any worries about taking ECP?</td>
<td>14%</td>
<td>21%</td>
<td>25%</td>
<td>27%</td>
<td>NS</td>
</tr>
</tbody>
</table>

| **N**                          | 21        | 287         | 159  | 188 |          |
| Do you feel you have           |           |             |      |     |          |
| sufficient information?        | 48%       | 54%         | 52%  | 57% | NS       |

*Knowledge about ECP and access to ECP*

Twenty four (11.5%) women who were seeking TOP before release of the ECP pack (group 1) had never heard of the ECP, compared with and 45 (14.6%) women who were seeking TOP 12 months after release of ECP, and
to 13 (6.4%) women who were seeking TOP 12 months after ECP became available over-the-counter (Table 6.7) (p=0.017).

Table 6.7. Knowledge about ECP and reasons for not being able to obtain ECP in responders.

<table>
<thead>
<tr>
<th>Knowledge about ECP</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=208</td>
<td>N=308</td>
<td>N=202</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes %</td>
<td>Yes %</td>
<td>Yes %</td>
<td>Yes %</td>
<td>0.02</td>
</tr>
<tr>
<td>Heard about ECP?</td>
<td>86</td>
<td>263</td>
<td>85.4</td>
<td>189</td>
</tr>
<tr>
<td>Received sufficient info</td>
<td>102</td>
<td>142</td>
<td>54</td>
<td>121</td>
</tr>
<tr>
<td>Ever taken ECP?</td>
<td>85</td>
<td>137</td>
<td>44.5</td>
<td>88</td>
</tr>
<tr>
<td>ECP taken to prevent this pregnancy?</td>
<td>14</td>
<td>29</td>
<td>9.4</td>
<td>22</td>
</tr>
<tr>
<td>Ever tried to get ECP but could not?</td>
<td>12</td>
<td>21</td>
<td>6.8</td>
<td>9</td>
</tr>
</tbody>
</table>

Women who had never heard of the ECP were of the same age as women who had already heard of ECP. The mean age of women who have never heard of ECP was 25.1 years in group 1, 27.5 years in group 2 and 26.8 in
group 3 in comparison to women who had heard of ECP, who were 25.6, 27.9, and 26.2 years of age in group 1, 2, and 3, respectively.

Half the women (101; 48.6%) who had heard of the ECP in group 1 stated that they had previously received sufficient information about ECP in comparison to 142 (53.8%) of women in group 2 and 122 (60.1%) women in group 3 (not significant; p=0.063).

Eighty three (39.9%) women in group 1, 137(44.5%) in group 2, and 88(43.3%) women in group 3 reported taking the ECP previously (p=0.579). Thus, the use of ECP had not increased significantly in the last few years and there was no increase in ECP use observed in women seeking TOP after ECP became available over-the-counter. Only 13 (6.3%) women in group 1, 21 (6.8%) in group 2, and nine (4%) women in group 3, attempted, but could not obtain ECP (p=0.529).

The mean age of women who had taken ECP previously was 25 years in group 1, 27 years in group 2 and 3, almost identical to the mean ages of 25, 28 and 27 years in women who have never taken ECP in group 1,2,3, respectively.

*Use of ECP*
Number of times the ECP was taken by responders is shown in Table 6.8. A small number of women (13(6.3%), 29(9.4%) and 22 (10.8%) in group 1, 2, 3, respectively) reported that they had taken ECP to prevent this pregnancy (p=0.241).
Table 6.8. Number of times ECP was used by women who presented for TOP before (group 1) and 12 months after a release of the ECP pack in Australia (group 2), and 12 months after ECP became available over the counter.

<table>
<thead>
<tr>
<th>No. of times ECP taken</th>
<th>Group 1 (n=208)</th>
<th>Group 2 (n=308)</th>
<th>Group 3 (n=202)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>1</td>
<td>48</td>
<td>23</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>7.7</td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>3.4</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>1.4</td>
<td>11</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>2.4</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>&gt;10</td>
<td>1</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Could not recall</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Never used</td>
<td>124</td>
<td>59.6</td>
<td>171</td>
</tr>
</tbody>
</table>
The distribution by age groups of number of times ECP was taken is shown in table 6.9.

Table 6.9. Number of times ECP was taken by women in different age groups who presented for TOP before (group 1) and 12 months after a release of the ECP pack in (group 2) and 12 months after ECP became available over-the-counter in Australia (group 3).

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Group 1 (n=208)</th>
<th>Group 2 (n=308)</th>
<th>Group 3 (n=202)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Age 13-19 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>taken ECP once</td>
<td>46</td>
<td>19</td>
<td>49</td>
</tr>
<tr>
<td>taken ECP more than once</td>
<td>11</td>
<td>23</td>
<td>11</td>
</tr>
<tr>
<td>Age 20-24 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>taken ECP once</td>
<td>69</td>
<td>36</td>
<td>69</td>
</tr>
<tr>
<td>taken ECP more than once</td>
<td>30</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Age 25-29 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>taken ECP once</td>
<td>45</td>
<td>26</td>
<td>70</td>
</tr>
<tr>
<td>taken ECP more than once</td>
<td>13</td>
<td>27</td>
<td>21</td>
</tr>
<tr>
<td>Age 30-34 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>taken ECP once</td>
<td>28</td>
<td>11</td>
<td>57</td>
</tr>
<tr>
<td>taken ECP more than once</td>
<td>4</td>
<td>8</td>
<td>19</td>
</tr>
<tr>
<td>Age 35-39 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>taken ECP once</td>
<td>17</td>
<td>8</td>
<td>42</td>
</tr>
<tr>
<td>taken ECP more than once</td>
<td>7</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Age 40-45 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>taken ECP once</td>
<td>6</td>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td>taken ECP more than once</td>
<td>1</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>
Table 6.10. Knowledge and accessibility of ECP by women 20 years and under and 21 years and over who presented for TOP before (group 1) and 12 months after a release of the ECP pack in Australia (group 2) and one year after ECP pack became available over-the-counter (group 3).

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=208)</th>
<th></th>
<th></th>
<th>Group 2 (n=308)</th>
<th></th>
<th></th>
<th>Group 3 (N=202)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>%</td>
<td>total</td>
<td>No</td>
<td>%</td>
<td>total</td>
<td>No</td>
<td>%</td>
</tr>
<tr>
<td>Heard about ECP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20 years</td>
<td>58</td>
<td>92.1</td>
<td>63</td>
<td>57</td>
<td>93.4</td>
<td>61</td>
<td>2</td>
<td>4.7</td>
</tr>
<tr>
<td>≥21 years</td>
<td>122</td>
<td>89.7</td>
<td>136</td>
<td>206</td>
<td>83.4</td>
<td>247</td>
<td>10</td>
<td>6.7</td>
</tr>
<tr>
<td>Total</td>
<td>180</td>
<td>90.5</td>
<td>199</td>
<td>263</td>
<td>85.4</td>
<td>308</td>
<td>12</td>
<td>5.9</td>
</tr>
<tr>
<td>Sufficient information about ECP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20 years</td>
<td>38</td>
<td>60.3</td>
<td>30</td>
<td>112</td>
<td>45.3</td>
<td>142</td>
<td>17</td>
<td>39.6</td>
</tr>
<tr>
<td>≥21 years</td>
<td>62</td>
<td>45.6</td>
<td>112</td>
<td>60</td>
<td>40.3</td>
<td>177</td>
<td>60</td>
<td>40.3</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>50.3</td>
<td>142</td>
<td>177</td>
<td>46.1</td>
<td>319</td>
<td>77</td>
<td>38.1</td>
</tr>
<tr>
<td>Ever taken ECP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20 years</td>
<td>26</td>
<td>41.9</td>
<td>23</td>
<td>48</td>
<td>37.7</td>
<td>71</td>
<td>28</td>
<td>65.1</td>
</tr>
<tr>
<td>≥21 years</td>
<td>59</td>
<td>43.4</td>
<td>114</td>
<td>80</td>
<td>46.2</td>
<td>219</td>
<td>80</td>
<td>53.7</td>
</tr>
<tr>
<td>Total</td>
<td>85</td>
<td>42.9</td>
<td>137</td>
<td>168</td>
<td>44.5</td>
<td>328</td>
<td>108</td>
<td>53.5</td>
</tr>
<tr>
<td>Taken ECP to prevent this pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20 years</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>8</td>
<td>8.2</td>
<td>2</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td>≥21 years</td>
<td>10</td>
<td>8</td>
<td>24</td>
<td>19</td>
<td>9.7</td>
<td>38</td>
<td>19</td>
<td>12.8</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>7</td>
<td>29</td>
<td>21</td>
<td>9.4</td>
<td>60</td>
<td>21</td>
<td>10.4</td>
</tr>
<tr>
<td>Ever tried to get ECP but could not</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20 years</td>
<td>7</td>
<td>5.3</td>
<td>16</td>
<td>8</td>
<td>6.5</td>
<td>10</td>
<td>5.4</td>
<td></td>
</tr>
<tr>
<td>≥21 years</td>
<td>17</td>
<td>8.7</td>
<td>21</td>
<td>8</td>
<td>6.8</td>
<td>25</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>8.7</td>
<td>37</td>
<td>16</td>
<td>6.9</td>
<td>35</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Doctor would not prescribe ECP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20 years</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>≥21 years</td>
<td>2</td>
<td>1.5</td>
<td>9</td>
<td>3.6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>3.5</td>
<td>9</td>
<td>3.6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Could not get to a doctor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20 years</td>
<td>3</td>
<td>4.8</td>
<td>3</td>
<td>4.9</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>≥21 years</td>
<td>4</td>
<td>3.0</td>
<td>7</td>
<td>2.8</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>3.5</td>
<td>10</td>
<td>3.2</td>
<td>1</td>
<td>0.5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Did not know where to got for ECP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20 years</td>
<td>2</td>
<td>3.2</td>
<td>2</td>
<td>3.3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>≥21 years</td>
<td>3</td>
<td>2.2</td>
<td>2</td>
<td>0.8</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>2.5</td>
<td>4</td>
<td>1.3</td>
<td>3</td>
<td>1.5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Did not know what to ask for</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20 years</td>
<td>2</td>
<td>1.5</td>
<td>2</td>
<td>3.3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>≥21 years</td>
<td>2</td>
<td>1.0</td>
<td>1</td>
<td>0.4</td>
<td>2</td>
<td>1.3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Other reasons for not getting</td>
<td>ECP</td>
<td>0-20 years</td>
<td>ECP</td>
<td>0-20 years</td>
<td>ECP</td>
<td>0-20 years</td>
<td>ECP</td>
<td>0-20 years</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-----</td>
<td>------------</td>
<td>-----</td>
<td>------------</td>
<td>-----</td>
<td>------------</td>
<td>-----</td>
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<tr>
<td>Total</td>
<td>3</td>
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<td></td>
<td></td>
</tr>
<tr>
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<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20 years</td>
<td>4</td>
<td>3.0</td>
<td>1</td>
<td>0.40</td>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥21 years</td>
<td>5</td>
<td>2.5</td>
<td>1</td>
<td>0.3</td>
<td>3</td>
<td>1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Twenty two (11%) women in group 1 had never heard of EC in comparison to 45 (15%) of responders in group 2, and 13 (6%) of responders in group 3. The women who had heard about EC were significantly younger (p<0.001). The mean age of women who had never heard of the ECP was 29.8 years compared to 26.3 years in women who had heard about ECP in group. There was significant difference in awareness about ECP between groups. More women were aware about ECP in group 3 (190 (93.6%)) in comparison to groups 1&2 (447 (86.6%), (p=0.008).

There was a statistically significant trend top increased use of the ECP in women of a higher educational level (p<0.005). On the other hand there was no significant difference in the number of women of different educational levels who had heard about ECP (p= 0.51), who reported having sufficient information about the ECP (p=0.66), who reported any concerns about taking the ECP (p>0.05), who took the ECP to prevent current pregnancy (p=0.79)or who had difficulties obtaining the ECP (p=0.19).

Twenty per cent of women in our study used ECP once, 11% used it twice, 4% used it three times, 2.5% used it four times and 1% of women used it five or more times (Table 6.8). Approximately half the women who had heard of the ECP stated that they had sufficient information about this regimen (Table 6.10).
A number of women were unwilling to use the ECP because they regarded it as unhealthy (21 (10.1%) in group 1, 46 (14.9%) in group 2, 18 (8.9%) in group 3) or had concerns about side-effects (40 in group 1, 62 in group 2, 28 in group 3). Their concerns centred on possible side-effects such as tiredness and lethargy, risk of breast cancer, blood clots, damage to the uterus, effect on long term health and future fertility and possible failure of EC. Five women felt that they had sufficient information about the ECP, but stated they did not know enough about it works. Finally, one woman stated that she did not agree with unneeded medications.

Overall, a small number of women (33; 6.3%) in our study reported that they were not able to obtain EC for a variety of reasons, e.g. a doctor would not prescribe, were not able to see a doctor, did not know where to go to get ECP, did not know how to ask for ECP or were overseas at the time they needed EC. Only 12 (6%) women in group 1, 21 (7%) in group 2, and nine (4%) women in group 3, attempted, but could not obtain the ECP (p=0.58) (Table 6.7).

*Concerns and worries about using ECP*

Approximately one third of women (74 (36%) in group 1, 82 (26.6%) in group 2, 35 (17.3%) in group 3) reported some concerns or worries about using ECP.

Only ten women in group 1 reported “other” concerns or worries about ECP. These included concerns about breast cancer, possible failure of ECP, not
knowing enough about how it works, insufficient information about ECP and concerns of tiredness and lethargy.

Seven women in group 2 reported concerns regarding ECP efficacy, two were concerned that they were not sure what ECP is, one woman was concerned that ECP may cause blood clots and may damage the uterus.

Two women in group 3 were concerned about the efficacy of ECP and not knowing how it works (Table 6.11).

Table 6.11. Concerns and worries about using ECP of women who presented for TOP before (group 1), 12 months after a release of the ECP pack (group 2) and 12 months after it became available over the counter in Australia (group 3).

<table>
<thead>
<tr>
<th>Concern</th>
<th>Group 1 (n=208)</th>
<th></th>
<th>Group 2 (n=308)</th>
<th></th>
<th>Group 3 (n=202)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Possible side effects</td>
<td>41</td>
<td>19.7</td>
<td>61</td>
<td>19.8</td>
<td>28</td>
<td>13.9</td>
</tr>
<tr>
<td>May effect long term health</td>
<td>15</td>
<td>7.2</td>
<td>35</td>
<td>11.4</td>
<td>13</td>
<td>6.4</td>
</tr>
<tr>
<td>May effect future fertility</td>
<td>15</td>
<td>7.2</td>
<td>32</td>
<td>10.4</td>
<td>9</td>
<td>4.5</td>
</tr>
<tr>
<td>Against religious or moral beliefs</td>
<td>3</td>
<td>1.4</td>
<td>2</td>
<td>0.6</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
6.4. Discussion

This study was undertaken to investigate the difference in knowledge and use of the ECP after it became more widely and easily available in Australia. The expectation was that availability of an ECP pack in Australia would increase community knowledge about ECP as well as its use. Abortion clinics provided an accessible source of sexually active women with possible motivation for using emergency contraception. Knowledge and use of EC by this group of women as well as barriers to its use and access could assist in developing programs to increase the use of EC. There were no significant demographic differences between the three study groups which suggested that comparison of knowledge, attitudes and use between the groups was valid and that they are representative of this population. However, the generalization of this study to the population of Australian women in the reproductive age groups is dubious as women with better knowledge and access to EC may have used it successfully to avert an unintended pregnancy.

Awareness of EC was already high before a dedicated pack became available in Australia and there is no indication from this study that marketing of an EC increased this. Among women who were seeking TOP prior to marketing 89% had heard about the EC compared to 85% of women who were seeking TOP 12 months after release of the EC on prescription. This is greater than 72% of women attending medical centre for abortions who were aware of EC in New Zealand in 1995 [106], but similar to 83% of women attending a clinic for
pregnancy counseling in Melbourne in 1999 [107]. In another questionnaire study undertaken in France 90% of 1365 women requesting abortions had heard about ECP, but only third had ever used it, and 9% used it in the cycle they became pregnant [108].

Among 623 women seeking abortions in India, where about 5-6 million abortions occur each year, most of them illegal, only 6 % have ever heard of the ECP and none had ever used it [109]. In Nigeria 58% of undergraduates knew about ECP, 34% had abortions in the past, but only 2 % had ever used it [110]. In a study published in 1999 on abortion seekers in Hong Kong 67% women knew about ECP, 10% had ever used it, and only 2.5% had used it to prevent the current pregnancy [111]. The designated LNG ECP pack became available in Hong Kong in 2002. In a study conducted in 2002 among married women, 71% of them had heard of ECP in comparison to 64% of women seeking abortion in a recent study [112].

A number of studies including our own have indicated that despite being aware of emergency contraception only a small percentage of women attending abortion clinics attempted to avert their current pregnancy by using ECP. In the 1999 Melbourne study only 9% of women used EC in attempt to prevent their current pregnancy in comparison to 9.2% in study from France [108], 3% in a Swedish study [113], 1.3% in the USA [88], and 1.1% in China [114]. There was a slight but non-significant increase in the number of women who had used
the ECP in an attempt to avert their present pregnancy as the ECP became more readily available in Australia (7%, 9%, and 11% of responders in groups 1, 2, 3, respectively). It does seem like the more recent study report higher frequency of ECP use by women. Introduction of ECP did increase awareness and use over the years – only 1% of women presenting for abortions in 1984 used ECP [115] in comparison to 7% in 1996 [116], 12 years after it was first licensed in the UK, and 10% in 2000 [117]. ECP was used by 12% of women seeking abortions in a Scottish study undertaken in 2005 [118]. ECP use appears to be among women who require it the most. On the other hand, women might have used it and did not present as ECP was effective.

In a recent study on the contraceptive usage, knowledge, and awareness of the usage among female emergency department patients in an urban academic hospital in the USA, prior usage of EC among women at risk of pregnancy and ever having an abortion, was associated with correct knowledge about the regimen. On the other hand, not having ever used EC was associated with not understanding its function. Participants of this study were mostly English-speaking white women who had generally good knowledge about contraceptive pill and condoms use, but very limited awareness about EC [119].

Older women were more likely than younger ones to be unaware of the EC. This suggests that the younger generation is better informed about current contraceptive options, probably through improved sex education programs in
schools. Several studies have found the same tendency to knowledge about the ECP in different age groups [107, 118, 120-123].

Forty three per cent of women in our study had taken an ECP previously, which is not significantly different from other studies. In a study from Melbourne 29 per cent of women seeking abortion had used the ECP in the past [107], 22 per cent in Sweden [113] and 53 per cent in New Zealand [106].

It has been shown that knowledge of emergency contraception improved significantly from 1984 to 1996. Thus, only 12% of women in 1984 had a good knowledge about emergency contraception in comparison to 73% in 1996 [116]. Therefore, authors stated that lack of awareness about emergency contraception was no longer an obstacle to its use and easier accessibility should be provided.

Level of education did not make any difference in knowledge and access to the ECP, however, women with higher educational level used the ECP in the past more frequently.

Concerns about health aspects and side effects prevented some women from accessing EC both in Australia and New Zealand [106]. One third of women in our study were concerned about using the EC. They were worried about possible side effects, breast cancer, blood clots, damage to the uterus,
tiredness and lethargy effect of EC on long term health and future fertility and failure of EC. In an attempt to provide a short succinct questionnaire to encourage completion we did not question the accuracy of women’s knowledge about the ECP. It is obvious that women need to be better informed about the EC and its side effects. Widely available accurate information addressing these concerns and widespread availability of affordable packets of the ECP could have prevented some of these unwanted pregnancies and would reduce unnecessary anxiety and increase use of this fertility control method in the future.

Rates of previous use of EC were lower in our study than in the Swedish study conducted when an ECP pack was available on prescription. Sixty-nine percent of the Swedes had used this method once, 23% twice, three women had used it three times, and four more than four times [113], which is considerably higher than in our study where only 20% had used the ECP once.

Many women (44%) in our study had previous abortions similar to a study of Swedish women where 43% of them reported having previous induced abortion [106, 113, 124]. This confirms that women who are seeking TOP are at higher risk of repeated abortions and they should receive sufficient information regarding ECP. It also indicates that this is a group of women who need encouragement to use more effective regular contraceptive methods. There
was no difference in number of previous abortions between women who had used and had not used ECP in the past.

In summary, introduction of a dedicated ECP pack on the Australian market and its availability over the counter does not appear to have increased women’s knowledge about ECP, and its use did not increase significantly among abortion seekers. The concerns women express about EC appear not to have lessened since the availability of a dedicated ECP pack, even though it is available over the counter. This suggests further studies are required to determine how best to inform women and allay their fears about EC. Although ideally, the aim should be for women and their partners to use effective regular contraceptive methods the very nature of sexual arousal and the sometimes unpredictable circumstances that lead to unprotected intercourse indicate that the use of EC should be encouraged by increasing knowledge and easy access to the ECP. The requirement of pharmacists to ask personal questions from women seeking the ECP in less than confidential surroundings may inhibit some pharmacists from supplying it and some women from requesting it.
4. GENERAL DISCUSSION and FUTURE RESEARCH

This study was set up to investigate the mechanism of action of ECP. There are several factors that make understanding of mechanism of action of ECP a very important subject. First of all understanding how ECP works may explain why it fails and how to use it to avoid this failure. Another important question that has been widely discussed in scientific and social literature is whether ECP works after fertilization occurred. If LNG ECP does not work after fertilization it would change its place in contraceptive options for many people who consider that human life begins at fertilization and will allow ECP to be used by more women. It is obvious that both of these issues may improve ECP use and therefore, decrease the number of unwanted pregnancies.

An improvement in awareness about ECP may be far more valuable in increasing its use. We attempted to achieve that through identifying social factors that should be addressed to improve the knowledge about and attitudes towards ECP in a group of women who would have contributed from the ECP the most, e.g. those who request termination of pregnancy.

It has been shown that ECP is very effective method to prevent unwanted pregnancy, though previous effectiveness studies concentrated on time period
between the unprotected sexual intercourse and ECP intake. However, ECP may work 4-5 days later after unprotected intercourse if it is taken before the ovulation. It does work in follicular phase of the cycle when folliculogenesis is in the process, but it does not work when it is taken around or after ovulation.

This study on a small number of patients for the first time demonstrated that ECP is highly effective if given before ovulation. One assumes that its efficacy is independent on when unprotected sexual intercourse occurred before ECP intake as long as ECP is taken before ovulation. It is not clear how long before ovulation it has to be taken to be effective, but it certainly does not work when taken after ovulation occurred. Therefore, other methods of EC, e.g. intrauterine device, should be considered in such cases.

It is obvious that for ECP to work it has to be used! And, for ECP to be used women should be aware about availability of this method. Our study revealed that wider availability of the ECP pack in Australia and an easier access to it has increased women’s awareness about the ECP. However, the use of ECP has not increased. There has not been an increase in a sell of Postinor in Australia despite of its easier access. One can assume that ECP use has not increased in this particular group of women who present for termination of pregnancy, but that may be different in other groups. It is re-assuring that there was an improvement in knowledge about ECP since it became more accessible (over the counter) in Australia. Another interesting observation of our study is
the fact that younger women are more aware of ECP. This finding suggests that targeting older women could improve knowledge about ECP and increase its use.

It is interesting that there was a relatively high awareness of the existence of ECP before a dedicated ECP pack became available. The actual usage of ECP in all three groups was low compared with awareness. Eighty nine per cent of women seeking termination of pregnancy before release of a dedicated ECP pack in Australia have heard about ECP, but only 41% used ECP in the past, and only 6% used it to prevent current pregnancy (Group 1). Eighty five percent of women seeking termination of pregnancy one year after release of a dedicated ECP pack have heard of ECP, 44% of women took ECP in the past, and seven percent took it to prevent current pregnancy (Group 2). Ninety four percent of women requesting termination of pregnancy one year after ECP became available over the counter (Group 3) were aware of ECP, 44% of women in this group have used ECP in the past, and 11% have taken it to prevent current pregnancy (Table 6.7). This is in step with reports from overseas (116, 117).

A larger study is required to confirm our findings on the mechanism of action of ECP. The failure rate of LNG ECP is low (3% in our study) and more pregnancies are required to assure that the findings statistically significant. Such study is underway in Chile.
8. 1. CONCLUSIONS

I. The mechanism of action of the LNG ECP is prevention of ovulation and it is not effective after ovulation has occurred. Three pregnancies that occurred in our study all happened when unprotected intercourse took place prior to ovulation and ECP was taken after the ovulation. On the other hand pregnancies has not established in cases when ECP was taken prior to the ovulation.

II. The LNG is effective when used for emergency contraception with the failure rate of 3% due to conceptions that occurred when ECP was taken just before or after the ovulation. This failure rate is probably an overestimate of the efficacy of ECP as conception depends on multiple factors, e.g. the viability of sperm and egg, the receptivity of endometrium and other factors that vary widely between couples and are unfeasible to encounter in such study.

III. The women's reports regarding the day of the menstrual cycle are not reliable. Fifty four per cent of women in our study had inconsistent results between the reports of the day of the cycle and their hormonal levels.
IV. There were no significant changes observed in awareness of women requiring termination of pregnancy about emergency contraception after ECP became more widely available after marketing of and EC in 2002 and more easily accessible after ECP became available over-the-counter in 2004. Unfortunately we did not observe in an increase in use of the ECP among abortion seekers.

V. Younger women are more aware about ECP and its use, which suggests that younger generation is better informed about current contraceptive options probably through improved sex education programs in schools.

8.2. RECOMMENDATIONS

I. Clients seeking the EC should be made aware of the mechanism of its action and it’s failure rate when taken just before or after ovulation and offered an alternative method of contraception (e.g. IUD) in such cases.

II. Clinicians should be aware that women’s recollection of the day of the menstrual cycle is unreliable. In practice, especially for research purposes, women’s reports about the day of the menstrual cycle should be confirmed with hormonal studies.
III. The older age group should be targeted in education campaigns on EC and prevention of unplanned pregnancy. The school would be still the most appropriate place for education about prevention of unplanned pregnancy as the majority of women who do have poor knowledge about ECP have only secondary education.
5. PUBLICATIONS related to this thesis


II. **Novikova N**, Weisberg E, Fraser I. Changes in knowledge and attitudes towards use of emergency contraception in abortion seekers as emergency contraception became more likely available in Australia. *In preparation.*
Appendix 1. Questionnaire on social and reproductive history that has been used in the study on the mechanism of action of emergency contraception pill

ID____________ Date __________ Time __________
Name_________________________ Phone ________________

1. What is your age?
2. Does your period occur regularly with the same number of days between each period (from 21 to 35 days)? Yes/No
3. How many days do you normally bleed with each period? ______
4. How many days does it usually take from the first day of bleeding of one period to the first day of bleeding of your next period)? ______
5. When was your last normal period (the date of the first day of bleeding)?____
6. When do you expect your next period to start? ______
7. How many hours ago did you have unprotected sex? _
8. Have you had any pregnancies before? Yes/No
   If yes, how many? ______
9. Have you had any miscarriages before? Yes/No
   If yes, how many? ______
10. Have you had any abortions before? Yes/No
    If yes, how many? ______
11. Have you given birth before? Yes/No
    If yes, how many times? ______
12. Have you ever used emergency contraception before? Yes/No
    If yes, how many times? ______
When did you use emergency contraception last time? ______
Did you get pregnant after taking emergency contraception? Yes/No
Appendix 2. Questionnaire that has been used in the study on the knowledge about and attitudes towards emergency contraception pill

**Emergency Contraception (morning after pill) Survey**

Thank you for agreeing to answer this questionnaire. We would like to find out how much you know about emergency contraception (the "morning after pill") and about your usual contraceptive practices. **This questionnaire is anonymous and there is no way that you can be identified from it.**

Please circle or tick the boxes

1. Have you ever heard about the "morning after pill"?     Yes/No

2. Do you feel you have enough information about the "morning after pill" to use it properly?     Yes/No

3. Have you ever taken the "morning after pill"?     Yes/No

4. If yes, how many times?_________

5. Did you take the "morning after" pill to try to prevent this pregnancy? Yes/No

6. Have you ever tried to obtain the "morning after pill" and couldn't to get it?     Yes/No

7. If yes, why couldn't you get it?
   • The doctor would not prescribe it
   • I could not get to a doctor in time
   • I did not know where to go for the "morning after pill"
   • I did not know what to ask
   • Other
   Please, specify _

8. Do you have any worries or concerns about taking the "morning after pill"?     Yes/No

9. If yes, what are the worries or concerns?
   o Possible side effects
   o It may affect my long term health
   o It may affect my future fertility
   o It is against my religious or moral beliefs
   Other, please specify ____________________________
10. What is your age? __

11. Have you had any pregnancies before? Yes/No
   If yes, how many? _____

12. Have you had any miscarriages before? Yes/No
   If yes, how many? _____

13. Have you had any abortions before? Yes/No
   If yes, how many? _____

14. Have you given birth before? Yes/No
   If yes, how many times? _____

15. What is your home postcode? ______

16. Which level of education have you completed?
   • Year 10 (school certificate)
   • Year 12 (higher school certificate)
   • Trade certificate eg TAFE
   • University or college degree
   • Post-graduate degree
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