Efficacy and Safety of Ultra Low Dose Oral Contraceptive Pills in Rural Indian Women - A Prospective, Open Label Study

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ABSTRACT

BACKGROUND

Combined oral contraceptive pills are the most effective temporary contraception methods and are used by approximately 60 - 80 million eligible women throughout the world. It is the oestrogen component of the combined oral contraceptive (COC) which is responsible for the undesirable and serious side effects such as deep vein thrombosis (DVT) and pulmonary embolism (PE). So, there has been a constant effort to reduce the amount of ethinyl estradiol (EE) while maintaining its contraceptive efficacy. This study was aimed at studying the safety and efficacy of ultralow dose combined oral contraceptive (containing 15 mcg EE + 60 mcg gestodene) in rural Indian women.

METHODS

The study was done at Rama Medical College, Mandhana, Kanpur, among 70 patients who fulfilled the inclusion criteria. The patients were given ULDOCP and followed up for 6 months. The patients followed the regime of one tablet of ULDOCP daily from day 1 to day 24 of the menstrual cycle with 4 days pill free period before starting the next pack.

RESULTS

Seventy patients completed the study till 3 months and fifty patients completed the study till 6 months. Break through bleeding (BTB) was the only prominent side effect which was reduced in subsequent cycles and our patients tolerated this well. No pregnancy resulted. The ULDCOP was very well accepted by those women who were counselled about possible side effects and their harmless nature before starting the study. It was found that the users were satisfied with the use of ULDOCP. All side effects were significantly lower after 2 months of use and there were no serious side effects.

CONCLUSIONS

The 24 / 4 ULDOCP regimen seems to be a safe and effective contraceptive method for use in rural population after properly counselling them. The reduced pill free interval of 4 days offered additional advantages.

KEYWORDS

Ultra-Low Dose Oral Contraceptive Pills (ULDOCP), Ethinyl Estradiol (EE), Safe Contraception, Gestodene, BTB (Break Through Bleeding)

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BACKGROUND

Contraceptives play a major role in reducing maternal mortality by reducing the risks of unsafe abortions, giving birth spacing and improving anaemias. Oral contraceptives have other non-contraceptive benefits like protection against endometrial and ovarian malignancies. It is the third most commonly used method of contraception in developing countries.

Over the years COCs have been the most widely used, convenient and cost-effective means of contraception. Oral contraceptive pills are classified according to the amount of EE contained in them into high dose COCS containing 50 mcg or more, low dose COCS containing 35 mcg to less than 50 mcg, ultra-low dose containing 15 to20 mcg EE. ULDOCPs are given in 24 / 4 regime and high dose are given in 21 / 7 regime. The research focus has been on reduction in EE and progestin to improve its tolerability and safety. The shorter pill free interval of 4 days is an added advantage as incidence of withdrawal symptoms are less and contraceptive efficacy is more. Progestins have been classified into four generations. First generation (pregnanes, estranes), second generation (desogestrel, levonorgestrel), third generation (gestodene, norgestimate) and newer progestins (drospirenone, dienogest). Oestrogen (EE) component of the COC is responsible for many side effects such as gastrointestinal (GI) upset, headache, migraine, weight gain, pigmentation, breast changes and BTB.

Many of these side effects though minor may not be acceptable to the users. Compliance of any contraception depends on its side effects. Certain major side effects like hypertension (HTN), DVT, venous thromboembolism (VTE) and PE were seen with high EE containing OCPs. A small but significant increase in the risk of breast cancer, liver cancer and adverse effects on metabolism were also seen. The side effects of EE are dose dependent. So, reduction in the dose of EE in COC was always sought after. Changing the composition of progestogen component also plays a major role. This ULDCOP contains gestodene, a third-generation progestin. It is more selective for P receptors, improves cycle control, metabolic changes and is the main factor in preventing pregnancy.

Objectives

Assessing safety and contraceptive efficacy with a fixed dose formulation of EE 15 micro grams and 60 microgram gestodene in a 24 / 4 regimen.

METHODS

This 'observational / interventional', prospective open label study was conducted at Rama Medical College, Mandhana, Kanpur over a period of one year from Jan 2018 to Dec 2018. The study was undertaken after ethical clearance from the institute's ethical committee. An informed consent was taken from all the participants. Women who attended Obstetrics and Gynaecology Outpatient Department (OBGYN OPD) who asked for or were advised oral contraception were considered. 94 rural women enrolled at the beginning but only 70 came for further follow up.

Sample Size

Sample size was calculated using Slovin's formula

$$N = N / (1 + Ne2)$$

Where, N is the required sample size, e = margin of error = 0.05 at 95 % confidence level and 1 = constant value. There were 122 OCP users in the previous year. Using this as N and e = 0.05 for 95 % confidence, sample size was calculated as 94. It was also decided to use convenience sampling method to select 94 cases, who were enrolled for ULDOCP but only 70 came for further follow up.

Inclusion Criteria

Were as per the World Health Organization (WHO) category 1 medical eligibility criteria.
Age: Menarche to 45 years.
Parity: Nullipara and parous.
Post abortion: First and second trimester and immediately post abortion.

Exclusion Criteria

Were as per WHO category 2 (use with caution) category 3 (avoid) and WHO category 4 (absolute contraindications) for the use of COCs. Such as

- Age more than 45 years
- Cigarette smoking
- Hypertension
- Diabetes
- Migraine
- Cardiovascular diseases
- History of thromboembolism
- Breast feeding
- Less than 6 weeks post-partum
- History of malignancies (breast and liver)

Study Protocol and Data Collection

Ultra-low dose oral contraceptive containing gestodene 60 microgram and ethinylestradiol 15 micro gram (brand name: Minesse Pfizer) was administered to 94 patients (enrolled for study) but only 70 turned up for follow up. Minesse is freely available in India at Rs 200 per pack to the patients and it was purchased by the patients. Records of patients were kept on many dimensions / parameters that are given below. Original patient records are property of Dept of Obstetrics and Gynaecology, Rama Medical College, Mandhana, Kanpur India. Age of patients varied from 18 to 45 years. History of medicines taken by patients that affected the efficacy of the ULDOCP was kept, and wherever the interaction was there (that is, the medicine being taken altered the effect of oestrogen), patients taking those medicines were excluded from study.

Patients who missed more than 2 tablets were later on excluded from the study. Each patient's weight, blood

pressure (BP), haemoglobin, serum glutamic oxaloacetic transaminase (SGOT) / serum glutamic pyruvic transaminase (SGPT), breast examination was done at the first visit. They started their medication from day 1 of the cycle and continued for 24 days. All patients were followed up at 1, 3 and 6 months. Out of 70 patients, 50 came up to 6 months and 20 patients did not come for further follow up. At each visit their weight, BP and physical examinations (including breast examination and bi manual examination) were done. Pap smear test was done before beginning the study.

Study Population
94 women volunteered between Jan 2018 to Dec 2018. 70 came for follow up till the next 3 months.

Compliance
All the 70 patients (for a period of 3 months) took the pills correctly, showing good compliance.

Contraceptive Efficacy
No pregnancy resulted in this study.

Safety
No serious side effects were seen in the study population. The most common side effect was breakthrough bleeding, followed in incidence were nausea, headache and breast tenderness.

Statistical Analysis
Evaluation was done by calculating percentages. For inferential statistics, 95 % confidence interval for the proportion has been calculated using standard error of proportion with z – value of 1.96.

RESULTS

		Out of 70	Percentage
Range of Age	18 - 25 years	12	17.14
	26 - 35 years	53	75.71
	36 – 45 years	5	7.1
Range of Weight	> 55 Kg	10	15
	45 - 55 Kgs	50	52
	< 45 Kg	10	14.28
Parity	Nullipara	10	14
	One	30	43
	> = Two	30	43

Table 1. Demographic Characteristics

Table 1 above shows the distribution of age, weight and parity. There are more patients in the 25 - 35 years age group. Very few that is 14 percent nullipara felt the need to use the ULDOCP whereas parous women contributed to 86 percent of the study population.

Reason	Out of 20	Percentage
BTB	2	10
Lost to follow up	10	50
Desirous of pregnancy	5	25
Nausea, heartburn	2	10
Headache	1	5

Table 2. Reasons for Discontinuation of Treatment

The adverse side effects for which the patients discontinued the medication were few BTB (10 %), nausea and heartburn (10 %), headache (5 %).

Parameter	Percentage of Patients		
	After 1 Month	After 3 Month	After 6 Month
Pregnancy reported	0	0	0
Breast tenderness	2	1	1
Break through bleeding	15	5	0
Spotting	5	2	0
Weight gain	0	0.2 to 0.3 Kg	0.3 Kg
Rise in BP	0	0	0
Nausea / vomiting	10	2	0
Headache	12	5	0
Painful menses	0	0	0
Emotional ability	2	1	0
Pain in abdomen	4	1	0

Table 3. Incidence of Side Effects

Incidence of side effects like breast tenderness, breakthrough bleeding, headache reduced over a period of 6 months. Percentages and their 95 % confidence interval have been calculated to assess side effects, reasons for non-continuation etc.

DISCUSSION

In general, use of OCPs in women of rural India is quite low because of many misconceptions, fears of side effects. Moreover, the use of COCs comes with gastritis in the initial phase which is quite a deterrent in continuing medication for long as they think, "this medicine is quite hard and is becoming a health hazard". So, they quickly stop the medicine despite repeated counseling. But once they find its beneficial effects like reduction in amount of menstrual flow, reduction in premenstrual syndrome (PMS), relief from dysmenorrhea then they follow the regime meticulously. It is more desirable to use ULDOCP in rural settings as they cannot come for frequent follow ups like breast examination and ultrasonography (USG) etc. The major reasons for discontinuation were side effects, wanting to conceive and doubts regarding return to fertility. So, counselling them beforehand regarding the great advantages against the very harmless, mild and reversible side effects greatly improved the compliance. They were educated regarding the missed pills and how to take care of the problem.

Previously it was believed that the contraceptive effect of a COC depends on its EE content, the more the EE better is the efficacy. Now studies have proved this wrong. It is believed that the progestin component is good enough to take care of contraception and EE takes care of cycle control. So, in future we can hope to reduce the content of EE even further in COC.

Ratnabali Chakraborti[1] (2001) reports a study of 20 microgram of oestrogen and 150 micrograms of desogestrel: they kept follow up of patients for 3 cycles; and found that results were good. Alfred P[2] (2001) discusses the emerging trend of using 20 micrograms oestrogen as OCPs.

In an article in American J (OBG Management; Robert LB.[3] (2011) it is noted that FDA has cautioned that women with migraine should not take ULDOCP as it is prone to cause headaches; also smoking women are also not to be given oestrogen based OCPs as it raises cardiovascular / stroke

risk. Here ULDOCP is helpful as low oestrogen reduces cardiovascular / stroke risk. On the same ground Calhoun et al.[4] (2017) argues that patients should go for 20 micro gram OCP rather than 30 micro grams oestrogen / progestin based OCP. A brief discussion on first (OCPs), second (LDOCPs) and third generation (ULDOCPs) OCPs.

Esra et al.[5] (2003) report use of ULDOCP in treatment of benign ovarian cysts. Alfred (2001) reports a study of efficacy of 20 micro gram oestrogen content in ULDOCP and finds that it results in pearl index (number of pregnancies in 100 women-year of treatment) of 0.88. In some cases of higher oestrogen dose, the pearl index shoots up to 2.1. In an African Study, E Van Der Westhuizen et al.[6] (2011) report the efficacy of low dose OCP.

In a European study, Creatsas et al.[7] (year not specified) discuss the pros and cons of ULDOCP but they do not give a detailed report of their field investigation. They note that ULDOCPs retain contraception efficiency and have reduced side effects. They had administered 15 microgram estradiol and 60 microgram gestodene.

It is felt that with the use of ULDOCP, the normal menstrual cycle resumes after a period of 4 - 6 months. This is found to be effective in several studies in Europe (Gestodene Study Group[8] 1999), Brazil (Ione B.[9] 2006) and Thailand (Ladakan J.[10] 2012). There are several internet resources that briefly describe the pros and cons of ULDOCP and LDOCPs. These are typically about 20 and 30 microgram EE based ULDCOPs.

David F Archer et al.[11] (2013: Obste & Gynae; 122 (3) p. 601 - 607) found that with the use of ULDOCP with 1 mg norethindrone and 10 microgram EE resulted in 26 pregnancies in a sample of 1555 women (resulting in pearl index of 2.2). Ahuja[12] has documented use of ULDCOP as new approach.

Mohan Ghule and Anita Raj[13] (year not given) documented that Indian rural women do not tend to use contraceptives.

The 13 references cited from scholarly journals are supplemented with internet references[14,15,16,17,18] (IR1 to IR5) that are popular articles written by medical practioners to sensitise the general public on the use of ULDCOP.

Thus, we see that there are few studies that have systematically investigated the usage of 15 micro gram oestrogen content of ULDOCP. This forms the motivation of present work.

CONCLUSIONS

ULDCOP offers a convenient, safe and effective contraception in the rural areas of developing countries like India. Since no pregnancy resulted as shown in our study, its contraceptive efficacy appears high. It shows that it is highly effective with reversible contraception. Since, it is highly acceptable to women (especially rural) they are likely to take it for a long term. It is quite cost effective and returning to fertility is much easier. There were no serious life-threatening side effects. The above study is first of its kind in India (15 mcg EE). In future comparison of performance of ULDCOP to performance of other OCPs must be done. It will be interesting to study the role of ULDCOP in hormone therapy (HRT), polycystic ovarian disease (PCOD), puberty menorrhagia and functional ovarian cyst (FOC).

Limitations of the Study

Inability to cover the required sample size is a limitation of the study. It was due to the fact that as of now general acceptance of OCPs is low in rural population.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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