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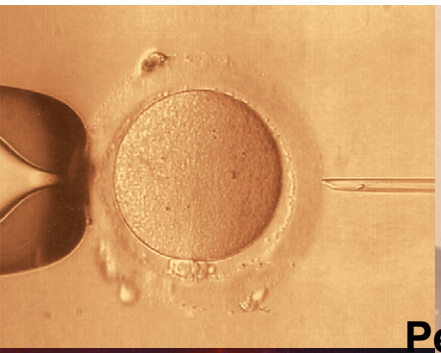

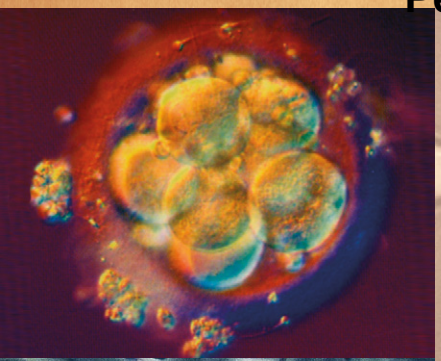

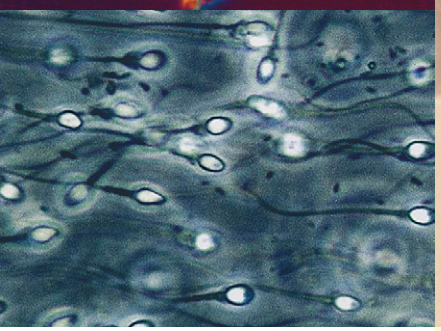

The Progestin-Only-Pill (POP) is not a Niche Option: New Preclinical and Clinical Data about the Interrelations between Levonorgestrel-Dosage Peripheral as well as Central Contraceptive Effects and Bleeding Behavior

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The Progestin-Only-Pill (POP) is not a Niche Option: New Preclinical and Clinical Data about the Interrelations between Levonorgestrel-Dosage, Peripheral as well as Central Contraceptive Effects and Bleeding Behavior

M. Oettel[1], P. S. Kochhar[1], H. Osterwald[1], M. S. Zarapkar[2], R. Walawalkar[3]

In preclinical studies with levonorgestrel (LNG) in rabbits and rats, we found that the pre-ovulatory as well as the post-ovulatory administration show no or only limited contraceptive activity. Therefore, the design of a progestin-only-oral contraceptive (POP) only on the base of non-ovulatory effects must be leading to sub-optimal results. On the other hand, elevation the dose above the ovulation-inhibition level can cause bleeding disturbances.

As a contribution for better clarifying these problems, a clinical proof-of-concept-study in a randomized, open-label, parallel group design was undertaken. The 20 volunteers included cyclic women that were divided in two groups. In group A (n = 10) the volunteers received daily 0.06 mg LNG over 56 days and in group B (n = 10) daily 0.09 mg LNG also over 56 days. The efficacy parameters were changes in progesterone plasma levels, urine pregnancy tests, behavior of cervical mucus, bleeding pattern and additionally evaluation of some parameters for safety and tolerability.

The results show that in the 0.06 mg group 3 of 10 women ovulated (plasma progesterone-monitoring) whereas in the 0.09 mg group none of the volunteers ovulated during the 20 treatment cycles. In no case, the urine pregnancy tests were positive. The investigation of the cervical mucus show consistently a score < 10, which was considered as "poor" or "unfavourable" for sperm penetration in either treatment arms. The bleeding pattern during the higher LNG-dosage treatment were better than in the lower dosage group (mean 1.6% bleeding days during 0.09 mg LNG vs. 3.6% in the 0.06 mg group). All the bleeding irregularities occurred only in the first month of treatment period. Tolerability and safety were satisfying in both groups.

These promising results must be confirmed in a suitable larger clinical study. **J Reproduktionsmed Endokrinol_Online 2015; 12 (4): 246–50.**

Key words: Progestin-only pill, levonorgestrel, dose-relationships between non-ovulatory and ovulatory contraception, bleeding behavior.

Introduction

The market for estrogens and progestins containing combined oral contraceptives (COCs) is critical because many variations are marketed. Furthermore, there are more than dozens of generic versions parallel on the market, this leaves only small profit margin. An original scientific breakthrough with this regimen of contraception is not on the horizon.

This is the reason why the R&D-activities worldwide are focussed on the following two topics:

Postcoital (Emergency) hormonal contraception including new antiprogestins/selective progesterone receptor modulators (SPRMs): The problem in this field is that the today known postcoital pills (Levonorgestrel 1.5 mg and Ulipristal 30 mg) have a clear lower contraceptive efficiency in comparison to the conventional COCs. The reason for the reduced effectiveness is the fact that both preparations do not work around the imminent ovulation date by not inhibiting the follicular rupture (Day –1/Day 0). But, 30% of the pregnancies begin within this window [1]. Therefore, an improvement of the postcoital contraception is possible only in the post-ovulatory period by influencing the fertilized eggs/blastocysts and by disturbing the implantation into the endometrium with all the ethic-moral discussions about the beginning of the life.

Progestin-only regimen: Whereas the non-oral routes for the progestin-only approaches were favoured (IUDs, implants etc.), the old daily LNG-containing progestin-only-pill (POP), e.g. with 0.03 mg LNG/day (Microlut®, 28 mini®), remains a niche-product despite the enormous advantage of not elevating the risk of thrombosis, which is the case with all major COCs currently on the market. The main reason that the LNG POP is such a niche market is its contraceptive efficacy and issues related to bleeding problems. The desogestrel-POP (Cerazette®) show better contraceptive effects based on the fact that it is prescribed dosage is above the ovulation-inhibiting level. But, bleeding behavior of the desogestrel-POP still problematic.

The aim of the work presented here was to re-examine the potential of the POP-principle. Is progestin-only-administration still a niche-option for contraception or is there the potential for a deeper change of the armamentarium for oral contraceptives? For our studies we selected LNG as a well known, well investigated reference compound with well established safety profile over long term use above what we propose here (both the traditional COC as well as the emergency contraception have significantly higher doses of LNG as compared to our regimen.

In preclinical studies using rats and mice, we studied the dose-relationships between ovulatory and non-ovulatory (peripheral) contraceptive effects.

Finally, in a clinical proof-of-concept study we looked into the dose relationships between ovulation inhibition and bleeding pattern in women.

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Table 1. Flow Chart of the Clinical Trial (Proof-of-Concept Study).

Activities	Visit 0 Day 10–3 (Run-in)	Visit 1 Day 0 First day of bleeding	Visit 2 Day 10	Visit 3 Day 20 ± 2 days	Visit 4 Day 30 ± 2 days	Visit 5 Day 48 ± 2 days	Visit 6 Day 56
Informed Consent	X						
Screening	X						
Medical examination	X	X	X	X	X	X	X
Laboratory Investigations	X						X
Serological Tests	X						
Urine Pregnancy Test	X			X		X	
Randomization & dispensing		X	X	X	X	X	
Plasma progesterone		X		X		X	
Vaginal mucus examination	X			X		X	
Safety Parameters			X	X	X	X	X
Protocol Compliance		X	X	X	X	X	X
Adverse Events			X	X	X	X	X
Monitoring			X	X	X	X	X
End of Therapy							X

Material and Methods

Preclinics:

1. Determination of pre-ovulatory contraceptive effects of LNG in adult New Zealand rabbits with body weight (b.w.) between 3000 and 4000 g.
   Day 1: Induction of follicle growth by s. c. injection of 50 I.E. pregnant mare's serum gonadotropin (PMSG) per animal.
   Days 2–4: Oral daily administration of 0.1 or 0.3 or 0.6 mg LNG/kg b.w.
   Day 4: Mating by fertile bucks (proof of sperms in the vagina) and after that ovulation induction by intravenous 100 I.E. Human Chorionic Gonadotropin (hCG) per animal.
   Day 6: Autopsy with counting of corpora lutea (or corpora rubra) and microscopic detection of fertilized and non-fertilized eggs after rinse of the tubes and uterus by isotonic saline solution. Biostatistical examination by Dunn-Test.
2. Determination of the post-ovulatory contraceptive effects of LNG in adult Wistar-rats with a body weight between 180 and 260 g. In rats, the oral bioavailability of progestins is poor [2]. Therefore, LNG must be given parenterally (in contrast to rabbits). Three female rats were placed in a cage with a male, who was checked for fertility previously. Vaginal smears were checked on daily basis for finding sperms in the vagina (Day 1). The mated females were separated from the buck and treated from day 1 to day 4 with 2, 20 or 200 mg LNG /kg b.w. subcutaneously. On day 10, autopsy with inspection of the uterus for counting the implantation sites was performed.
3. Determination of antigonadotrophic action of LNG in Wistar rats. Immature male Wistar rats (35–50 g b.w.) were gonadectomized under hexobarbital anaesthesia and treated subcutaneously with daily 0.2 or 0.6 or 2 mg LNG/kg b.w. over 14 days. On day 15, blood was withdrawn from abdominal aorta (urethane 1200 mg/kg b.w.) and rat luteinizing hormone (rLH) was determined by double antibody radioimmunoassay according the instructions of NIAMDD. Biostatistical significance was determined using one-way analysis of variance (ANOVA).
4. Clinical Study. A clinical Proof-of-Concept Study was designed as a randomized, parallel group end point trial to assess the clinical feasibility of two dosages of levonorgestrel in a progestin-only-pill-regimen (POP) in healthy adult female subjects of childbearing potential with normal ovulatory cycles [3]. This trial was conducted in compliance with Good Clinical Practice (GCP) at a site inspected and approved by the USFDA and regulatory authorities from Europe. Approval by the Independent Ethics Committee, Thane/India, was given on July 29th, 2013.

We chose 20 healthy women aged 18–40 years who were already on combined oral contraceptives (COCs) regimes that allow a pill-free- or placebo-interval of seven days. The women were asked to commence study medication on the first day of their bleeding (after stopping the COC). This date was day 1 of the study. Table 1 shows the flow chart of the trial.

This study was conducted using a randomized, open-label, parallel group design. The 20 included subjects were divided into two groups in 1:1 manner, i.e. n = 10 for Group A and n = 10 for Group B.

Group A: The subjects received in the morning 2 tablets of LNG 0.03 mg, which means 0.06 mg per day over 56 days.

Group B: The subjects received in the morning 3 tablets of LNG 0.03 mg, which means 0.09 mg per day over 56 days.

The **efficacy parameters** were:

- Change in the plasma progesterone levels throughout the study. Elevated concentrations over 5 ng/mL indicate an ovulation.
- Behavior of the cervical mucus according to the system adopted by World Health Organization [4]. A mucus score of 15 is defined as optimal for sperm penetration; 10–14 is good and a score < 10 is poor or non-favorable for sperm passage.
- Bleeding Pattern. Bleeding irregularities occur more frequently with the use of POPs than with COCs. Therefore, the subjects were provided with diaries to record daily the bleeding

Table 2. Determination of pre-ovulatory contraceptive effects of levonorgestrel (LNG) in adult New Zealand-Rabbits.

Daily oral dosage of LNG (mg/kg) over 3 days before induced ovulation	n	Corpora lutea (mean)	Total number of eggs vs total number of fertilized (cleaved) eggs	%
Control (Sesame oil)	32	14.4	351 vs 318	90.6
0.1 mg LNG	9	12.6	92 vs 78	84.8
0.5 mg LNG	9	10.0	81 vs 49	60.5
2.5 mg LNG	8	14.8	112 vs. 61*	54.5

* $p < 0.05$ vs control

Table 3. Determination of post-ovulatory contraceptive effects of levonorgestrel (LNG) in adult Wistar-Rats.

Treatment subcutaneously on days 1–4 after mating	Daily LNG dosage/kg b.w.	Number of treated animals vs number of intact pregnancies	Pregnancy inhibition (%)
Control (Sesame oil)	–	12 vs 12	0
LNG	0.5	12 vs 12	0
LNG	5.0	12 vs 12	0
LNG	50.0	11 vs 11	0

Table 4. Suppression of serum rat luteinizing hormone (rLH) by levonorgestrel in gonadectomized male Wistar-Rats (means ± Standard Error of means; S.E.M.).

Group	Daily dosage, subcutaneously over 14 days	Rat Luteinizing Hormone (rLH) ng/mL serum and standard error of means (S.E.M.)
Control, intact (n = 9)	Sesame oil	14.6 ± 2.0
Control, gonadectomized (n = 7)	Sesame oil	228.0 ± 23.5
Levonorgestrel (n = 6)	0.2 mg/kg	210.0 ± 26.0
Levonorgestrel (n = 7)	0.6 mg/kg	12.2 ± 3.6*
Levonorgestrel (n = 8)	2.0 mg/kg	5.0 ± 0.9*

* $p < 0.05$ vs gonadectomized control

patterns throughout the trial, which include frequency, duration and intensity of bleedings.

– Safety and Tolerability Evaluation: Regular safety evaluations, such as vital signs and adverse event monitoring was done at each visit of the volunteers. Hematology, clinical chemistry and urine status (routine and microscopically) were examined at the screening-period and at the end of treatment. A treatment-emergent adverse event was defined as unfavorable or abnormal finding that was not present at baseline or, if present in baseline, increased in severity as the treatment progressed. Serious adverse events were defined as those immediately life-threatening are permanently or significantly disabling, requiring a prolonged hospitalization, resulting in long-term out subject treatment, or in congenital anomaly, cancer, or death. Any subject who had received at least one administration of the trial drug was evaluated from point of safety.

Results

Using the model of induced ovulation by PMSG s.c. and hCG i.v., the pre-ovulatory administration of oral LNG to rabbits reduces significantly the number of fertilized (cleaved eggs) in the tubes or uterus only in the high dosage of daily 2.5 mg/kg LNG (Tab. 2). This dosage lies clearly over the oral ovulation-inhibition level of 0.5 mg/kg LNG in naturally paired rabbits [5].

In principle, we found the same relationships giving LNG s.c. post-ovulatory to female Wistar-Rats. Even the extremely high dosage of daily 50 mg/kg s.c. on days 1–4 after mating has had no any effect on the pregnancy rate (Tab. 3). In contrast to this, the low daily dosage of 0.6 mg/kg reduced significantly the serum LH-concentrations (Tab. 4).

A numerical overview concerning the subject population shows the following:

– Planned volunteers for completion: 20
– Enrolled and randomized: 20
– Dropouts: none
– Withdrawals: none
– Completed as per protocol: 20
– Subjected to laboratory investigations including urine pregnancy test: 20
– Subjected for safety evaluation: 20

Table 5 shows the plasma progesterone levels (ng/mL) recorded at baseline on day 0 (visit no. 1; V1), day 20 (visit no. 3, V3), and day 48 (visit no. 5; V5).

In Group A (0.06 mg/day) three from 10 women (volunteers S-1; S-5; S-15) ovulated once or twice during the treatment period indicated by plasma progesterone levels > 5 ng/mL.

In Group B (0.09 mg/day) all of the 10 volunteers showed progesterone values < 5 ng/mL indicating no ovulations. Volunteer S-18 had a plasma progesterone of 13.09 ng/ml at day 0, i.e. before starting the medication. However, after starting the treatment in this volunteer, the

progesterone plasma levels were consistently recorded at 0.13 or 0.41 ng/mL indicating no ovulation.

As shown in Table 6, the cervical mucus score was consistently below 10, which was considered as "poor" or "non-favorable" to sperm penetration in either treatment arms with the exception of Subject S-15 in Group A and Subject S-13 in Group B, who had a cervical mucus score of 10 at visit 3.

At visits 3 (day 20) and 5 (day 48), none of the subjects in either treatment group showed positive urine pregnancy tests.

The summary of the bleeding pattern are shown in Tables 7 and 8. Comparing the two dosage groups, the bleeding pattern during the higher dosage of LNG-treatment is unexpectedly better than in the lower dosage group (mean 3.6% bleedings days during 0.06 mg LNG/day vs. 1.6% during 0.09 mg/day). In no case the bleeding behavior was the reason for finishing the study prematurely, hence, all patients finished the study.

All the bleeding irregularities in both groups showed low intensity (spottings) and occurred only in the first month of the treatment period.

There were no serious adverse events (SAEs) recorded during the course of the trial. Two single adverse events (AEs) were counted (nausea/dizziness and scanty bleeding). No therapeutic or pharmacological treatment was required. Both the AEs recovered without sequel.

Table 5. Plasma progesterone concentrations (ng/ml) on days 0 (V1), 24 (V3) and 48 (V5).

Group A (0.06 mg/day)				Group B (0.09 mg/day)			
Subject No.	**V1**	**V3**	**V5**	**Subject No.**	**V1**	**V3**	**V5**
S-1	0.15	6.10	3.72	S-2	n. m.	n. m.	N .m
S-3	0.10	0.20	0.12	S-4	0.11	n. m	n. m.
S-5	0.20	5.08	5.69	S-7	0.12	0.11	0.12
S-6	0.15	0.10	0.18	S-8	0.19	n. m.	n. m.
S-9	0.11	n. m.	0.10	S-10	0.13	0.22	n. m.
S-11	0.10	0.11	n. m.	S-12	0.13	n. m.	n. m.
S-14	0.14	n. m.	n. m.	S-13	0.25	n. m.	n. m.
S-15	10.94	0.15	12.04	S-16	0.00	n. m.	n. m.
S-17	n. m.	n. m.	0.15	S-18	13.09	0.13	0.41
S-20	0.25	0.28	0.15	S-19	0.11	n. m.	n. m.

n. m. = not measurable (under detection limit)

Table 6. Cervical mucus examination score on days 20 (V3) and 48 (V5).

Group A (0.06 mg/day)			Group B (0.09 mg/day)		
Subject No.	**V3**	**V5**	**Subject No.**	**V3**	**V5**
S-1	5	4	S-2	6	6
S-3	5	8	S-4	6	4
S-5	5	6	S-7	4	6
S-6	6	7	S-8	3	5
S-9	7	9	S-10	7	6
S-11	7	6	S-12	5	6
S-14	5	4	S-13	10	8
S-15	10	8	S-16	8	6
S-17	6	5	S-18	9	8
S-20	3	5	S-19	6	5
Mean	5.9	6.2	Mean	6.4	6.0
SD	1.9	1.8	SD	2.2	1.2

Discussion

The POPs were developed in the mid-1960s, when it was discovered that small doses of progestins could prevent pregnancy, mainly without ovulation inhibition but based on changes to the cervical mucus, endometrium and tubal motility [6]. But from the beginning of this developments the greatest disadvantages of POP were reduced contraceptive efficiency in comparison to the oral combined contraceptives (COCs) and bleeding irregularities occurred up to 47.5% of treated women [7]. Therefore, POP has been described as "a limited alternative for certain women" meaning a useful method for women in whom estrogens are contraindicated (e.g. women with elevated thrombotic risk like smokers, diabetics and overweight women), for older women and for nursing mothers [8].

Our preclinical data show that in order to influence all the peripheral contraceptive mechanisms much higher dosages of LNG are necessary than for inhibition of ovulation. These findings underline that the main mode of action of the post-coital or emergency contraception with LNG must be inhibition of ovulation and not pre- or post-ovulatory peripheral mechanisms.

Therefore, the aim of the here presented clinical proof-of-concept study was to determine the effects of a POP-regimen with higher LNG-dosages on ovulation (central action), cervical mucus (peripheral action) and – most important – on bleeding behavior of cyclic women.

For considering dose-efficiency-relationships the study was designed with two arms (0.06 mg LNG/day and 0.09 mg LNG/day over 56 days).Whereas in the 0.06 mg/day group three from ten women ovulated once or twice in the 56 days-period, the pattern of the cervical mucus in this group reflected a total block for the sperm penetration through the cervix.

In the 0.09 mg group no women ovulated and the behavior of the cervical mucus did not allow sperm penetration. Using urine pregnancy test, it was evident that none of the women in both groups were pregnant. In the textbooks, the ovulation inhibition dosage for LNG is indicated with 0.06 mg/day [9]. In our study, we found ≤ 0.09 mg/day. The reason for that could be methodological and/or ethnic differences.

Table 7. Bleeding Pattern during 56 days treatment period in Group A (0.06 mg/day); low intensity bleedings (spottings) occurred only in the first 28 days.

Subject No.	Bleeding Days	Percentage of Bleeding Days During 56 Treatment Days
S-1	No bleedings	0%
S-3	3 days single	5.4%
S-5	4 days single	7.1%
S-6	No bleedings	0%
S-9	No bleedings	0%
S-11	5 days single	8.9%
S-14	1 day	1.8%
S-15	1 day	1.8%
S-17	No bleedings	0%
S-20	6 days single	10.7%

Table 8. Bleeding Pattern during 56 days treatment period in Group B (0.09 mg/day); low intensity bleedings (spottings) occurred only in the first 28 days.

Subject No.	Bleeding Days	Percentage of Bleeding Days During 56 Treatment Days
S-2	No bleedings	0%
S-4	No bleedings	0%
S-7	5 days single	8.9%
S-8	No bleedings	0%
S-10	No bleedings	0%
S-12	No bleedings	0%
S-13	4 days single, only scanty	7.4%
S-16	No bleedings	0%
S-18	No bleedings	0%
S-19	No bleedings	0%

The observed bleeding pattern is not in correspondence to the actual teaching. The suggested inverse relationship between inhibition of ovulation and cycle regularity [10] obviously did not exist in our study. With other words: The assumption that higher dosages of LNG cause more bleeding irregularities is not underlined by our clinical results. Even 0.09 mg LNG/day resulted in a better bleeding profile than intake of 0.06 mg/day.

Lakha et al [11] reported the bleeding behavior during the daily intake of 0.03 mg levonorgestrel (to date the "normal" levonorgestrel POP). They found that from 23 women none were amenorrhoeic. 39% of the women bled or spotted for five or more days per month and four women withdrew from the study prematurely because of continuous irregular bleeding. These unfavourable characteristics couldn't be found with the higher daily dosages of 0.06 or 0.09 mg LNG/day in our study.

These findings open new perspectives for a new LNG containing POP. The contraception with this principle is suitable for all fertile women who wish family planning. Nevertheless, the LNG-dosage of 0.09 mg LNG/day is lower than the lowest dosage in the well known LNG-containing COCs which are distributed world-wide.

Another advantage of the LNG-POP: The risk of thromboembolic events in desogestrel-containing COCs is higher than in LNG-containing COCs [12]. Additionally, it is discussed that the androgenic side effects of LNG are responsible for a good cycle control and reduced proliferative action [13]. Therefore, we can assume with some caution, that LNG could be the progestin of choice for POP [14].

These findings and arguments can be also helpful to make a higher dosed LNG-POP to a candidate for the first OTC (over-the-counter without prescription) oral contraceptive [15, 16].

But all the advantages of a higher dosed LNG-POP which were presented and discussed in this paper possess an important reservation: Our clinical study is to small for making safe conclusions. Depending from the authorities, this will not be possible before finalizing a larger clinical study.

Conflict of Interest

M. Oettel, P. S. Kochhar, H. Osterwald are connected with Naari AG/Basel-Switzerland which is sponsor of all presented studies. M. S. Zarapkar is employee of LifeSan Clinical Research/Mumbai/India, and R. Walawalkar works at Snehal Hospital in Thane/India. As principal investigator or investigator they are partly responsible of the clinical work presented in this publication.

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