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Effect of BMI and body weight on pregnancy rates with LNG as emergency contraception: analysis of four WHO HRP studies

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Abstract

Objective

To estimate the effect of increased body weight and body mass index (BMI) on pregnancy rates with levonorgestrel (LNG) 1.5 mg used as emergency contraception (EC).

Methods

The study reviewed data from 6873 women in four WHO-HRP randomized trials on EC conducted between 1993 and 2010. Participants took either 1.5 mg of LNG as a single dose or in two doses 12 h apart, up to 120 h of unprotected intercourse. Contraceptive efficacy (pregnancy rates) at different weight and BMI categories was evaluated.

Results

Overall pregnancy rate was low at 1.2%. Pregnancy rates were also low in women weighing over 80 kg (0.7%) and who were obese (BMI over 30 kg/m^2) (2.0%). The pooled analyses for pregnancy demonstrated that BMI over 30 kg/m^2 decreased efficacy significantly (odds ratio 8.27, 95% confidence interval = 2.70–25.37) when compared to women in lower BMI categories, mainly influenced by pregnancies in obese women from one study site. Sensitivity analyses excluding that site showed that obesity was no longer a risk factor; however, the other studies included too few obese women in the sample to exclude a substantial decrease in efficacy.

Conclusions

Pregnancy rates with use of LNG 1.5 mg for EC were low at less than 3% across different weight and BMI categories. Pooled analyses showed an increase in pregnancy rates among obese women (BMI more than 30 kg/m^2) compared to women with normal BMI levels, influenced by pregnancies all coming from one study site.

Implications

Access to LNG as EC should still be promoted to women who need them, and not be restricted in any weight or BMI category, with additional attention for counselling and advice for obese women.

Keywords: Emergency contraception, Hormonal contraception, Levonorgestrel, Body weight, Body mass index (BMI)

1. Introduction

Reasons for using emergency contraception (EC) include possible contraceptive method failure or a possible incident of unprotected sex. Among the factors that affect the risk of pregnancy with use of levonorgestrel (LNG) as EC are the timing of drug intake in relation to intercourse, additional acts of intercourse after drug intake and the day of the cycle intercourse took place. LNG 1.5-mg pill is the most common method of EC and can be usually taken up to 120 h after an unprotected intercourse [1].

The finding that LNG as EC may be less effective in women with increased body mass index (BMI) was highlighted in the paper by Glasier et al. [2]. The analyses of pooled data came from two studies — the first had 773 participants who took LNG as EC up to 72 h after unprotected intercourse, and the second had 958 participants who took it up to 120-h delay. The reported pregnancy rates with LNG 1.5 mg were 2.5% [95% confidence interval (CI), 1.3%–4.6%] in overweight (BMI of 25–30 kg/m^2) and 5.8% (95% CI, 3.5%–9.5%) in obese (BMI≥30 kg/m^2) women while it was only 1.3% (95% CI, 0.8%–2.2%) in normal and underweight women (BMI<25 kg/m^2). Other covariates in the analyses that were significantly associated with pregnancy risk included the probability of conception at time of intercourse and having additional acts of intercourse after EC intake. There were concerns whether these results on the use of LNG as EC can be applied in women of higher weight outside of the US and the UK where these studies were conducted.

Another report by Kapp et al. which analysed the same data on the 1731 participants from these two studies showed that LNG was less efficacious in preventing pregnancy in women with higher body weight and higher BMI [3]. The estimated pregnancy rate increased four- to fivefold in higher weight categories or with increased BMI. This further supports the need for the question on whether the regimen of LNG 1.5 mg as EC was useful in preventing pregnancy in the higher weight and BMI categories and possibly in varied population settings.

From 1993 to 2010, the United Nations Development Programme (UNDP)/United Nations Population Fund (UNFPA)/United Nations Children's Fund (UNICEF)/World Health Organization (WHO)/World Bank Special Programme on Research and Research Training in Human Reproduction (HRP) conducted four randomized clinical trials involving the use of LNG 1.5 mg for EC [4], [5], [6], [7]. In these studies, treatment groups used LNG either as a single dose of 1.5 mg of LNG or as a double dose of 0.75 mg of LNG given within a 12-h interval. Two of the trials were multicentre studies in collaborating sites from Africa, Asia, Australia, Europe and Latin America [5], [6]. The other two trials were single-country studies in Hong Kong and Nigeria [4], [7]. Features of the studies are summarized in Table 1. Participants were healthy women with regular menses, not using other hormonal contraception and requesting EC within 120 h (as defined in the respective trials) of an unprotected act of intercourse. The main outcome was pregnancy. Piaggio et al. previously published an analysis regarding the effect of delay in administration of LNG for EC on pregnancy rates [8].

An analysis of a subset of these studies [5], [6], [7] by Gemzell-Danielson et al. in 2015 reported 56 pregnancies among 5812 women who received EC within 72 h following unprotected intercourse and did not find any increased risk of pregnancy with increasing bodyweight and BMI [9]. Limitations reported in the paper include the low number of women in the higher weight and BMI group. Obesity was not among the initial factors considered for recruitment in the initial studies.

This present paper provides an analysis of the data from the four studies supported by WHO HRP, building upon the earlier analyses [8]. Pooling data from these trials includes more women from several countries across the globe for analyses of the relationship between weight and BMI with the efficacy of LNG 1.5 mg as EC.

2. Methodology

This report combines data involving 6873 women with available outcome details, who had received 1.5 mg of LNG for EC up to 120 h after an act of unprotected intercourse. In each of the four studies, participants were randomized to EC regimens as described in Table 1.

For the pooled analyses, all available potential factors — (a) treatment dose; (b) delay of treatment since unprotected intercourse; (c) age; (d) weight; (e) BMI; (f) outcome of previous pregnancies; (g) conception probability; (h) further acts of intercourse; and (i) time of drug intake relative to the day of ovulation were fitted in the statistical modelling. Body weight and height were measured in all studies using standard clinic scales (H. v. Hertzen personal communication, November 07 2014, and O. A. Dada, personal communication, March 2 2015). We included both body weight and BMI in the logistic regression models with pregnancy as the outcome.

These studies were conducted in different time periods and settings. We evaluated "study" as a four-level random effect, looking at how much variation in the treatment outcome exists between the studies. This approach differs from the Gemzell-Daniellson analyses which looked at the grouping of participants from continents or geographic regions [9]. The multilevel analysis technique implemented with the SAS® Mixed and GlimMix procedures was applied and introduced study in the multilevel model as a random effect parameter. The calculated intraclass correlation coefficient (ICC) yielded a very small value of 0.0041 which indicates that only 0.41% of the variability in treatment outcome is accounted for by the studies, with the rest of the variability to be accounted for by the patient-level characteristics. We also analysed for study type (single-country vs. multicentre), resulting in even lower ICC of 0.0004 that is only 0.04% of the variability in treatment outcome. Study and study type were not statistically significant effects with p-values 0.151 and 0.286, respectively. When pooled analyses showed significant findings affecting outcome which was assessed to be mainly coming from one site, a sensitivity analysis was done excluding data from that site.

The calculations and statistical modelling were performed with the SAS® system v.9.3 using logistic regression analysis with stepwise selection. All the explanatory variables mentioned previously were included in the modelling, with weight and BMI categorized into commonly used levels.

3. Results

The analyses included 6873 women (of the 7164 reported as being in the LNG arms in the four studies) who had complete data regarding treatment details and the outcome (which was a positive pregnancy test result about 1 week after a missed menstrual bleeding and confirmed with an ultrasound examination). Table 2 describes the main demographic characteristics of the women included, showing the variations in the distribution of weight and BMI grouping across the studies, ranging from 0.2% to 7.4% for women weighing over 80 kg, and from 1.2% to 8.2% for women with BMI over 30 kg/m^2. There was only 1 woman out of 410 in the HK study over 75 kg, while in the Nigeria study, 405 out of 2794 women weigh 75 kg or more. In the HK study, only 6.6% of participants had BMI above 25 kg/m^2 (overweight and obese), while in the Nigerian study, the percentage was 36.8%.

3.1. Assessment of pregnancy rates in major risk categories

Table 3 shows the treatment outcome by major risk factors that are generally considered for the LNG EC efficacy analysis. The overall pregnancy rate remains low in all the studies, at 1.2% (0.9–1.5), with a range of 0.6 (in the Nigerian study) to 2.9% (in the Hong Kong study, which also had the least sample size). The rates remained low among women weighing over 80 kg (0.7%; 0.1%–2.7%) and who were obese (2.0%; 0.8%–4.6%). The pregnancy rates among the different BMI categories showed low rates with wide CIs with the upper range from 13.3 to 43.9% because of the very few numbers in these groups. The pregnancies in the higher BMI groups were only found in the WHO 2002 study and the study in Nigeria.

3.2. Adjusted regression model

Table 4 shows the adjusted regression model showing that BMI over 30 kg/m^2 or obesity provides a significant effect on efficacy (Odds Ratio [OR] = 8.27, 2.70–25.37). Weight categories (as shown in Table 3) got removed from the model. Other factors that were significantly associated with reduced efficacy in the model were delay in drug intake more than 48 h, additional acts of intercourse after drug intake and taking the drug at the time of or after ovulation. This finding of the effect of obesity was mainly due to the pregnancies in women from the study site in Nigeria. There were no other pregnancies in this category from the other studies. Sensitivity analysis performed on the pooled subset without the Nigerian study data excluded high BMI as a risk factor; however, this would now be based on a much smaller number of women in this group (Table 4a).

Table 5 shows the obese women by pregnancy status and day of treatment related to ovulation. All of the obese women who became pregnant (all from Nigeria) took the emergency contraceptive pill after the expected date of ovulation. This supports the increased efficacy of the drug if taken shortly before or at the expected date of ovulation, based on its biological effect of preventing ovulation [10].

4. Discussion

The four WHO HRP studies provided a large amount of data on LNG as EC on about 7000 patients worldwide [4], [5], [6], [7]. This provides an important opportunity to address the question of whether and how much weight or BMI affect pregnancy rates after EC use. High BMI was among the main factors that affected efficacy of EC, based on the modelling in this analysis.

The HRP studies were conducted in different times (from 1993 to 2010) and did vary by coverage (single country and multicentre). We looked at the pooled data as a hierarchical or multilevel data with four potentially different clusters. Having hierarchical data means that the data can be grouped according to factors (time period when the studies were conducted, or type of study — single vs. multicountry, etc.) that usually introduce “intra-cluster homogeneity” and “between-cluster heterogeneity.” It can be assumed that within each study, data were homogeneous as much as defined by a study protocol. Our analyses did not find “study” and “study type” as significant factors, implying that perceived variations in the study characteristics may not have contributed to the outcome.

There were some unique features in the original reports of the individual studies. These four studies were already analysed together to see the effect of treatment delay on the pregnancy rates [8]. The issue of obesity was not taken into consideration in this analysis. The proportion of obese women in the Nigeria study is 8.2% (229/2794), while in the other three studies it is only 1.6% (65/4079). Thus having the data from the Nigeria study increases the proportion of obese women in the pooled dataset to 4.3% (294/6873) for evaluation. This provided an important opportunity to address the question of whether and how much weight or BMI affect pregnancy rates after EC use. Other features of the Nigeria study included lower reported rates of using EC because of possible condom failure (19.8–20.3% vs. 44–46%) and a higher likelihood of participants being lost to follow-up compared to the women in the 2002 WHO study (6.6% vs. 1.5%) [6], [7]. This was also considered in the analyses by Gemzell Danielsson, noting the unique features of these women from this subset.

The initial pooled analysis shows that women of the BMI obese category are at much higher risk (effect size more than 8) of pregnancy compared to the normal weight women. These results were consistent with the previously cited reports [2], [3] expressing the higher risk. The analyses by Gemzell Danielsson who reported ORs relative to the BMI and weight categories, with a single significant effect OR = 2.18 (95% CI, 1.03 to 4.62) appearing at BMI 44 kg/m^2 and body weight 80 kg [8].

Based on the pooled analyses, we noted that our findings were mainly due to pregnancies reported in the obese women from the Nigeria study site. This may have implications on generalizability of results to other populations and to subgroups of populations. The sensitivity analyses of the pooled data, excluding the Nigeria data failed to show that BMI affected efficacy; however, there were few obese women in the other studies. Thus, one cannot exclude a large effect of obesity on the pregnancy rate (Table 4a).

As far as weight and BMI are concerned, across the defined weight and BMI categories, the rates of pregnancies remain low and were below 3.0%. The limitation of this pooled analysis is that all four studies were not originally intended to be stratified in the randomization according to weight or BMI of patients.

5. Summary and conclusions

LNG 1.5 mg for EC results in pregnancy rates less than 3% across different body weight and BMI categories. There was an observed decrease in effect among obese women compared to women with normal BMI levels. This was highly influenced by treatment results in women from one subset of the study population. The pregnancy rates in the various categories for users of LNG as EC are still low, and provision of LNG should not be restricted in any weight or BMI category based on these data. While there may be other options for EC, LNG remains the most widely available drug for EC.

The latest recommendations in the Medical Eligibility Criteria for contraceptive use (fifth edition) do state that women who are obese can use LNG as Emergency contraceptive pills without restriction (Medical Eligibility Criteria for Contraceptive Use Category 1). ECPs may be less effective among women with BMI≥30 kg/m^2 than among women with BMI<25 kg/m^2. Despite this, there are no safety concerns [11]. Apart from weight and BMI, there are other factors to consider when taking EC, such as timing of when to take LNG 1.5 mg as EC, in relation to the sexual act, and to the day of ovulation. Counselling and information on proper use should be provided.

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Figures and Tables

Table 1

Characteristics of WHO EC trials using LNG

Trial	EC regimen used in trial	Participating centres in countries	Number of LNG cases included in this analyses (sample size)
A. Hong Kong 1993 [4] A prospective randomized comparison of LNG with Yuzpe regimen; Delay 0–48 h	Two LNG 0.75-mg doses with 12-h interval	1 centre in Hong Kong	410 (440)
B. WHO 1998 [5] RCT of LNG versus Yuzpe regimen; Delay 0–72 h	Two LNG 0.75-mg doses with 12-h interval	21 centres in 14 countries	974 (1001)
C. WHO 2002 [6] Low-dose mifepristone and two regimens of LNG; Delay 0–120 h	One LNG 1.5 mg dose Two LNG 0.75-mg doses with 12-h interval	15 centres in 10 countries	2695 (2756)
D. Nigeria 2010 [7] A randomized double-blind study to compare two regimens of LNG; Delay 0–120 h	One LNG 1.5 mg dose Two LNG 0.75-mg doses with 12-h interval	7 centres in Nigeria	2794 (3022)
Total pooled data	One LNG 1.5 mg dose Two LNG 0.75-mg doses with 12-h interval	31 centres in 17 countries	6873 (7219)

Table 2

Demographic characteristics of participants from the included individual studies

Study and sample size	**Hong Kong 1993 (*n*=410)**	**WHO 1998 (*n*=974)**	**WHO 2002 (*n*=2695)**	**Nigeria 2010 (*n*=2794)**	**Total pooled data (*n*=6873)**
1. Mean age (SD)	26.6 (6.1)	27.3 (7.0)	27.2 (7.1)	26.6 (5.9)	27.0 (6.6)
2. Mean weight in kg (SD)	51.9 (6.6)	58.4 (10.4)	56.2 (8.7)	63.2 (10.5)	59.1 (10.3)
3. Weight categories, *n* (%)					
3a. Weight in kg < – 75	408 (99.8%)	901 (92.5%)	2609 (96.8%)	2384 (85.5%)	6302 (91.8%)
3b. Weight in kg 75–80	0	35 (3.6%)	35 (1.3%)	198 (7.1%)	268 (3.9%)
3c. Weight in kg 80 ++	1 (0.2%)	38 (3.9%)	51 (1.9%)	207 (7.4%)	297 (4.3%)
4. Mean height in cm (SD)	158.4 (6.7)	162.9 (6.4)	163.0 (6.1)	162.1 (7.5)	162.4 (6.9)
5. BMI categories as kg/m^2, *n* (%)					
5a. BMI (<– 25)	378 (93.3%)	821 (84.3%)	2469 (91.6%)	1760 (63.1%)	5428 (79.1%)
5b. BMI [25–30)	20 (4.9%)	127 (13.0%)	194 (7.2%)	799 (28.6%)	1140 (16.6%)
5c. BMI [30 ++)	7 (1.7%)	26 (2.7%)	32 (1.2%)	230 (8.2%)	295 (4.3%)

Table 3

Pregnancy rates in various categories of weight and BMI from the included individual studies

Study and sample size	Hong Kong 1993 (410)	WHO 1998 (974)	WHO 2002 (2695)	Nigeria 2010 (2794)	Total pooled data (6873)
Number of pregnancies	12	10	44	17	83
Pregnancy rate	2.9 (1.3–4.6)	1.0 (0.4–1.7)	1.6 (1.2–2.1)	0.6 (0.3–0.9)	1.208 (0.95–1.47)
Pregnancies (N,%) by weight (kg) group					
a. Weight < – 75	11/408 (2.7%)	10/901 (1.1%)	44/2609 (1.7%)	14/2384 (0.6%)	79/6302 (1.3%)
b. Weight [75–80)	0	0/35 (0.0%)	0/35 (0.0%)	1/198 (0.5%)	1/268 (0.4%)
c. Weight [80 ++)	0/1 (0.0%)	0/38 (0.0%)	0/51 (0.0%)	2/207 (1.0%)	2/297 (0.7%)
Pregnancies (*N*, %) by BMI (kg/m^2) group					
a. BMI (<– 25)	10/378 (2.6%)	10/821 (1.2%)	42/2469 (1.7%)	6/1760 (0.3%)	68/5428 (1.3%)
b. BMI [25–30)	0/20 (0.0%)	0/127 (0.0%)	2/194 (1.0%)	5/799 (0.6%)	7/1140 (0.6%)
c. BMI [30 ++)	0/7 (0.0%)	0/26 (0.0%)	0/32 (0.0%)	6/230 (2.6%)	6/295 (2.0%)

Table 4

Analyses of combined of four WHO HRP studies looking at number of pregnancies, pregnancy rates

Variable (all four studies)		Number of pregnancies	Number of women	Pregnancy Rate (%)	Odds ratio (95%C.I.)
BMI	(< 25) kg/m^2	68	5428	1.25	1.00 (Ref)
	[25–30) kg/m^2	7	1140	0.61	0.96 (0.42–2.21)
	[30 ++) kg/m^2	6	295	2.03	8.27 (2.70–25.37)

Table 4a

Analyses of combined of three WHO HRP studies looking at number of pregnancies, pregnancy rates (excluding data from Nigeria)

Variables (excluding data from Nigeria)		Number of pregnancies	Number of women	Pregnancy rate (%)	Odds ratio (95% CI)	
BMI	(<25) kg/m^2	62	3668	1.69	Eliminated	
	[25–30) kg/m^2	2	341	0.59		Eliminated
	[30 ++) kg/m^2	0	65	0.00		

Note.
Other factors that were shown to significantly affect pregnancy rates include delay in treatment more than 48 h, further acts of pregnancy and timing of drug intake in relation to time of ovulation (at day 0 and later).

Table 5

Risk of pregnancy among obese women in the four studies

Study and pregnancy status of obese participants		Day of drug intake relative to day of ovulation						All
		Before		On the day		After		
		n	%	*n*	%	*n*	%	*n*
WHO 1998 (92908)	Not pregnant	7	26.9	9	34.6	10	38.5	26
WHO 2002 (97902)	Not pregnant	11	34.4	1	3.1	20	62.5	32
Hong Kong 1993	Not pregnant	3	42.9			4	57.1	7
Nigeria 2010 (A15062)	Not pregnant	56	25.1	33	14.8	134	60.1	223
	Pregnant					6	100.0	6
Total	Not pregnant	77	26.8	43	14.9	168	58.3	288
	Pregnant	0	0	0	0	6	100.0	6