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Effect of body weight and BMI on the efficacy of levonorgestrel emergency contraception☆,☆☆

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Abstract

Objectives: To further evaluate the effect of weight and body mass index (BMI) on the efficacy of levonorgestrel emergency contraception.
Methods: Data from two large, multicenter, randomized controlled trials designed to assess emergency contraceptive efficacy were pooled to evaluate the effect of weight and BMI on pregnancy rates among women who received levonorgestrel. Descriptive methods (comparison of means and distributions according to pregnancy status and pregnancy rates across weight and BMI categories) as well as cubic spline modeling were used to describe the relationship between pregnancy risk and weight/BMI.
Results: The analysis population comprised 1731 women, among whom 38 pregnancies were reported. Women for whom levonorgestrel was not effective in preventing pregnancy had a significantly higher mean body weight and BMI than women who did not become pregnant (76.7 vs. 66.4 kg, $p<.0001$; 28.1 vs. 24.6 kg/m^2, $p<.0001$). The estimated pregnancy rate increased significantly from 1.4% [95% confidence interval (CI): 0.5%–3.0%] among the group of women weighing 65–75 kg to 6.4% (95% CI: 3.1%–11.5%) and 5.7% (95% CI: 2.9%–10.0%) in the 75–85 kg and >85 kg groups, respectively. Statistical modeling demonstrated a steep increase in pregnancy risk starting from a weight near 70–75 kg to reach a risk of pregnancy of 6% or greater around 80 kg. Similar results were obtained for statistical modeling of BMI as well as when the two studies were analyzed individually.
Conclusions: All analyses showed a significant drop in the efficacy of levonorgestrel emergency contraception with increasing body weight, with pregnancy risk in the higher weight categories similar to expected rates in the absence of contraception. Like body weight, increasing BMI was highly correlated with increased pregnancy risk.
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Keywords: Emergency contraception; Hormonal contraception; Levonorgestrel; Efficacy; Body weight; Body mass index

1. Introduction

Levonorgestrel (LNG) is a well-established and widely used treatment to prevent pregnancy after an act of intercourse which was unprotected or inadequately protected by a contraceptive method. LNG at a dose of 1.5 mg was registered as an emergency contraceptive based on the results of World Health Organization-sponsored clinical trials conducted primarily in the developing world [1,2]. Since first becoming available 15 years ago, LNG has become available without prescription in most countries around the world given its well-characterized safety profile and the importance of intake as soon as possible after unprotected intercourse.

Ulipristal acetate (UPA) was developed more recently as a novel emergency contraceptive. In the course of the UPA development program, a series of large-scale prospective clinical efficacy trials were conducted in the United States and Europe, two of which included a LNG comparator arm. Such randomized controlled trials thereby provide data on the efficacy of LNG in a contemporary Western population. In comparison with previous studies [1,2] in which LNG was estimated to prevent at least 80% of expected pregnancies [85% (95% confidence interval [CI]), 74%–93%] and 80% [95% CI, 71.2%–85.6%], respectively), in these two trials, LNG prevented 69% (95% CI, 46%–82%) and 52.2% (95%

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CI, 25.1%–69.5%) of expected pregnancies, suggesting a lower effectiveness rate of LNG than in previous reports. Similarly, a recent study, which utilized hormonal measurements of the fertile window rather than relying on presumptive menstrual data, estimated an effectiveness of LNG for emergency contraception (EC) of 68% [3].

The question of whether body mass index (BMI) or weight might influence the efficacy of EC was first raised in a 2011 analysis that examined prognostic factors for risk of pregnancy using the same pooled database [4] and showed that LNG when taken for EC among overweight or obese women had decreased efficacy in preventing pregnancy. The relationship was highly statistically significant, similar to that seen with established risk factors such as further unprotected intercourse and intercourse during the fertile window (conception probability). Before this publication, increased weight/BMI had not been previously described as negatively impacting the emergency contraceptive effect of LNG.

As such findings have important implications for the counseling and clinical management of women seeking and using EC, we performed further statistical analyses of this data set [4] to thoroughly describe the relationship between LNG efficacy (pregnancy rate) and body weight/BMI.

2. Materials and methods

Data from the two randomized controlled trials with a LNG comparator arm that were carried out in the course of the development of UPA were pooled [5,6] to increase the overall sample size and maximize the ability to detect any effect of body weight on pregnancy rates. The first study [5] enrolled women from seven investigational sites in the United States, and the second [6] included women from 35 investigational sites in the United Kingdom (10 sites), Ireland (1 site) and the United States (24 sites). Both studies were designed to demonstrate the noninferiority of UPA treatment compared with LNG among healthy women seeking EC after unprotected intercourse (defined by lack of contraceptive use, condom breakage or other barrier method failure). Inclusion criteria for both studies were unrestricted in terms of body weight and BMI; however, to be eligible, women had to report a history of regular menstrual cycles (24–35 days long), a negative pregnancy test at enrollment and no current or recent use of hormonal contraception. Follow-up was scheduled approximately 1 week following the next expected menstrual period, at which time systematic urine pregnancy testing was performed.

The two studies had a similar design with three key exceptions: the time window for EC intake following unprotected intercourse, the LNG dosing regimen and the manner in which weight and height were reported. In the Creinin study, unprotected intercourse must have taken place within 72 h of seeking EC, while this timeframe was increased to within 120 h in the Glasier study. The LNG dosing regimen used was two doses of 0.75 mg LNG taken 12 h apart in the Creinin study and 1.5 mg in one dose in the Glasier study. The two LNG dosing regimens have been shown in the literature to have similar effectiveness in a head-to-head clinical efficacy comparison [2]. Finally, body weight and height were measured in the Creinin study and self-reported in the Glasier study.

The analyses were conducted on the primary efficacy evaluable populations as specified in each study protocol. This population corresponds to women who received LNG, had a known efficacy outcome (pregnancy status) and whose pregnancy did not precede drug intake. The efficacy evaluable population as defined in the Glasier study included women aged ≤ 35 years, while the Creinin study's efficacy evaluable population included women aged >35 years. We compared the two data sets for demographic homogeneity and assessed for interaction between studies. Additionally, we assessed for any correlation between possible confounding factors previously described in this data set [4] and in the literature and as prognostic factors for treatment failure (conception probability calculated according to Trussell et al. [7], and further acts of unprotected intercourse after intake). Conception probability for the study population was calculated using the cycle day of intercourse relative to the expected ovulation for each woman enrolled [7,8].

To assess the effect of weight and BMI on pregnancy rates, several complementary analyses were performed. The first statistical analysis compared the weight and BMI of women found to be pregnant versus those who were not pregnant following LNG treatment. The second analysis estimated the pregnancy rate in five prespecified classes of weight and BMI. The first two methods were not adjusted for major confounding factors (study effect, further unprotected intercourse and conception probability), but the relationship between the variables and the weight or BMI was estimated (e.g., correlation between conception probability and weight).

A logistic model including known confounding factors (study, further unprotected intercourse, conception probability) and the dichotomization factor (high vs. low weight and BMI) while maximizing the R^2 of the model was retained to provide the best description of data assuming a stepwise relationship. Finally, cubic spline logistic regression modeling was performed to create a smoothing of the shape of the unadjusted relationship between weight/BMI and pregnancy rates [9]. This method utilizes five predictions of the pregnancy rates corresponding to five percentiles (the first, third, fifth, seventh and ninth deciles) of the distribution of the data.

3. Results

The primary efficacy evaluable populations from the two studies included 1731 women randomized to receive LNG, among whom 38 pregnancies were reported. The pregnancy rate was 1.7% ($n=13$) and 2.6 % ($n=25$) in the Creinin and

Glasier studies, respectively. Demographics and prognostic factors of EC failure in the study populations are presented in Table 1. The mean weight of the overall, pooled population was 66.6 kg, which was not significantly different between the two studies (p=.68); however, the mean BMI of 24.7 kg/m^2 showed a significant difference of 1.0 kg/m^2 (p=.001) between the two studies (Table 1).

Weight was neither significantly related to conception probability nor to further unprotected intercourse in the pooled analysis; similarly, BMI was not related to conception probability or further unprotected intercourse. There was no significant difference in the pregnancy rates between studies (study effect) and no significant interaction between study and weight or BMI (no significant difference in the relationship between pregnancy rates and weight or BMI across studies).

3.1. Comparison of body weight and BMI according to pregnancy status

The difference in the mean weight between women found to be pregnant at follow-up (76.7 kg) compared to those not pregnant (66.4 kg) was significant (10.2 kg±2.5, 95% CI 5.3–15.1), as was the weight distribution between these two groups (p<.0001) in the pooled analysis (Fig. 1). Similarly, the mean BMI of 28.1 (±6.6) was significantly greater for those pregnant at follow-up than for those who were not 24.6 (±5.4) (p<.0001). Accordingly, the distribution of BMI among these two groups was also significantly different (p<.0001) (Fig. 2).

3.2. Assessment of the relationship between pregnancy and weight/BMI category

The differences in estimated pregnancy rates by weight categories demonstrated a highly significant increasing trend (p<.001, stratified Cochran Armitage trend test). There was a marked increase in pregnancy rate between the three lowest weight categories (ranging from 0.9% to 1.4%) and the two highest weight categories: 6.4% (3.1%–11.5%) and 5.7% (2.9%–10.0%) in the 75–85 kg and >85 kg groups, respectively (Table 2).

Pregnancy rates by BMI category similarly demonstrated a highly significant increasing trend across increasing BMI categories (p=.007, stratified Cochran Armitage trend test) (Table 3).

3.3. Assessment of the effect of weight and BMI on pregnancy rates using logistic regression

Multivariate logistic models relating pregnancy risk with weight, adjusted for further unprotected intercourse, and conception probability showed a significant effect of weight in the Creinin study (p=.0476) and the Glasier study (p=.003). When the two studies were pooled and the study effect was added in the multivariate model, the relationship between pregnancy rate and weight was even more significant (p=

Table 1
Demographics and potential confounding factors of efficacy-evaluable population in the two studies analyzed.

	Study		
	Creinin, 2006 (*N*=773)	Glasier, 2010 (*N*=958)	Total (*N*=1731)
Weight (kg)			
Mean±SD (min, max)	65.9±14.7 (34.5, 136.0)	67.2±15.7 (39.5, 158.8)	66.6±15.3 (34.5, 158.8)
Categories, *n* (%)			
<55 kg	154 (20)	195 (20)	349 (20)
55–65 kg	288 (37)	320 (33)	608 (35)
65–75 kg	194 (25)	232 (24)	426 (25)
75–85 kg	61 (8)	94 (10)	155 (9)
≥85 kg	76 (10)	117 (12)	193 (11)
BMI (kg/m^2)			
Mean±SD (min, max)	24.1±5.2 (15.4, 54.7)*	25.1±5.6 (14.9, 53.7)*	24.7±5.5 (14.9, 54.7)
Categories, *n* (%)			
<20	118 (15)	131 (14)	249 (14)
20–25	421 (54)	452 (47)	873 (50)
25–30	147 (19)	220 (23)	367 (21)
30–35	52 (7)	97 (10)	149 (9)
≥35	35 (5)	58 (6)	93 (5)
Age (years), mean±SD	24.3±5.7	23.6±4.7	23.9±5.2
Race, *n* (%)			
Caucasian	566 (73)	692 (72)	1258 (73)
Black	110 (14)	175 (18)	285 (17)
Asian	52 (7)	19 (2)	71 (4)
Other	45 (6)	72 (8)	117 (7)
Conception probability (7)	5.37%	5.50%	5.44%
Further unprotected intercourse, *n* (%)	31 (4.0)	51 (5.3)	82 (4.7)
Time between unprotected intercourse and intake (h), mean±SD	35.3±21.6	39.7±25.7	37.6±24.1

* p=.001.

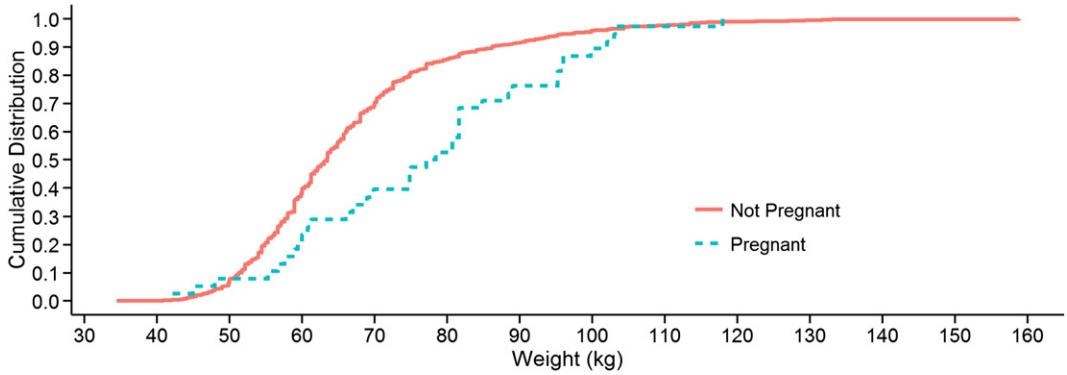

Fig. 1. Cumulative frequency distribution of weight according to pregnancy status post-intake of LNG.

.0003). Additional models including interaction terms between weight or BMI and other known predictors were fitted to assess whether the effect of weight or BMI depended upon the level of other confounding factors. There was no significant interaction between weight or BMI and further acts of unprotected intercourse (p=.572 and p=.267 for weight and BMI, respectively) and between weight of BMI and conception probability (p=.786 and p=.544, respectively). Additionally, there was no interaction between weight (p=.975) or BMI (p=.310) and study, suggesting a consistent relationship across the two studies.

3.4. Assessment of the effect of weight and BMI on pregnancy rates using cubic spline logistic regression

The cubic spline logistic regression demonstrated that the predicted probability of pregnancy increased from about 2% at a body weight near 70 kg to a pregnancy risk of 6% or greater, around 80 kg (Fig. 3). The risk plateaued near 6%, at a pregnancy rate which reflects the study population's overall estimated conception probability in the absence of contraception. The two studies similarly demonstrated a dramatic increase in pregnancy rates as weight increases from 70 to 80 kg when the regression was applied to each study individually, reflecting the homogeneity of these data sets (Fig. 3).

The same analytical approach was applied to BMI: a steep increase in pregnancy rates began at a BMI of 26 kg/m^2 and plateaued around 31–32 kg/m^2 (Fig. 4) at a pregnancy risk close to 5%; a similar relationship was present when the regression was applied to each study individually (Fig. 4).

3.5. Combining weight and BMI thresholds

The estimated pregnancy rates in various possible subgroups of women below the weight of 75 kg (Table 4) but with exceeding various values of BMI remained below 2%. In these data, BMI does not provide additional information regarding the efficacy of LNG once body weight has been considered.

4. Discussion

Analyses of 1731 women included in two randomized comparative trials consistently demonstrated an increased risk of pregnancy following LNG EC among women with higher body weights and BMIs. These results were consistent between analyses using several statistical techniques. Pregnancy rates increased steeply for women weighing between 70 and 80 kg who used LNG for EC. BMI was found to have a similar relationship to pregnancy rates as body weight, with efficacy increasing sharply around

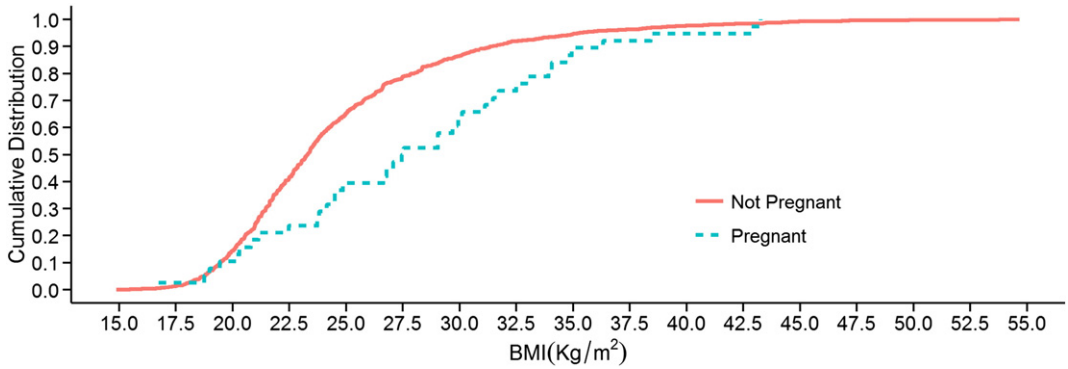

Fig. 2. Cumulative frequency distribution of BMI according to pregnancy status post-intake of LNG.

Table 2
Pregnancy rate following LNG EC according to weight categories.

	Weight (kg)				
	<55	55–65	65–75	75–85	≥85
N total	349	608	426	155	193
N pregnancies	3	8	6	10	11
Pregnancy rate	0.9%	1.3%	1.4%	6.4%	5.7%
95% CI[a]	0.2–2.5	0.6–2.6	0.5–3.0	3.1–11.5	2.9–10.0

[a] Exact Clopper Pearson method.

26 kg/m^2, but did not appear to modify estimated pregnancy rates beyond predictions based on body weight alone. The strengths of these analyses include the use of a large data set representing a contemporary Western population familiar with the use of EC, and the homogeneity of the results between the two high-quality, similarly designed studies contributing to the pooled data. The relationship between weight/BMI and pregnancy rate is consistent between these studies, as demonstrated by their similar logistic regression results and similarly shaped regression curves with a steep increase in pregnancy rates between 70 and 80 kg.

The most important limitation of these findings is that they are the result of exploratory analyses conducted using data from trials not designed to address whether weight impacts the ability of EC treatment to prevent pregnancy; however, these analyses can be seen as hypothesis-generating which would ideally be confirmed in other contemporary data sets. Additionally, although the data set is large, including more than 1700 women, the total number of women and pregnancies in the highest weight categories is small. Despite these limitations, the shape of the relationship between LNG efficacy and weight is consistent between the two individual studies and clearly illustrates a steep increase in pregnancy rate between a body weight of 70 and 80 kg. Above 75–80 kg, the observed pregnancy rate is similar to the expected pregnancy rate of the study population.

Body weight and height were measured at inclusion in one of the clinical studies [5] and were self-reported in the other [6], meaning that a little more than half (55% of the overall database) of these data were self-reported. Although there is a risk that women underreport their weight, these two databases were analyzed separately and found to reflect similar relationships between pregnancy rates and weight/BMI.

Confounding factors were addressed in several analyses, and none were found to have a correlation with weight or BMI. In this database, time to LNG intake following unprotected intercourse was not found to be a prognostic factor for treatment failure and therefore was not considered in the adjusted logistic regression model in which other variables known to be confounding factors were included.

Decreased efficacy in higher weight women has been reported for other hormonal therapies. A systematic review of the evidence on the effectiveness of hormonal contraceptives among overweight and obese women found mixed reports of an association; however, higher pregnancy risk, whether in women with BMI >25 kg/m^2 (combined oral contraceptive) or body weight >70–80 kg (contraceptive patch, vaginal ring, implant) [10], was reported in some studies. Effectiveness may be related to metabolic changes associated with obesity or with increasing body mass or adipose tissue, but as many contraceptive studies exclude overweight women, this issue has not been well studied. Therefore, the underlying mechanisms by which a higher body weight or body mass may reduce contraceptive efficacy remain unclear. That decreased effectiveness has been reported for multiple hormonal methods, including for long-acting hormonal contraceptives for which user compliance is not in question, indicates that such an effect is likely to be a real one.

It is unlikely that heavier women are underdosed with LNG for EC. Although no study specifically investigating pharmacokinetic and pharmacodynamic parameters following LNG administration in average, overweight and obese women is available, a randomized pharmacodynamic trial that reported ovulation in women who received a half-dose (LNG 0.75 mg), full dose (LNG 1.5 mg) or placebo in the follicular phase demonstrated that the two LNG doses were equipotent in disrupting ovulation [11]. Follicular rupture failed to occur during the 5-day period following dosing in 44%, 50% and 36% of cycles with the standard dose, half dose and placebo, respectively, and ovulatory dysfunction, characterized by follicular rupture associated with an absent, blunted or mistimed gonadotropin surge, occurred in 35%, 36% and 5% of standard dose, single dose or placebo cycles, respectively. Indeed, very early publications on the minimal effective dose report that even a single dose of 0.4 mg LNG could be sufficient to cause ovulatory dysfunction [12]. These data lead to the conclusion that lower serum levels of

Table 3
Pregnancy rate following LNG EC according to BMI categories.

	BMI (kg/m^2)				
	<20	20–25	25–30	30–35	≥35
N total	249	873	367	149	93
N pregnancies	4	11	9	10	4
Pregnancy rate	1.61%	1.26%	2.45%	6.71%	4.30%
95% CI[a]	0.44%–4.06%	0.63%–2.24%	1.12%–4.60%	3.26%–11.99%	1.18%–10.64%

[a] Exact Clopper Pearson method.

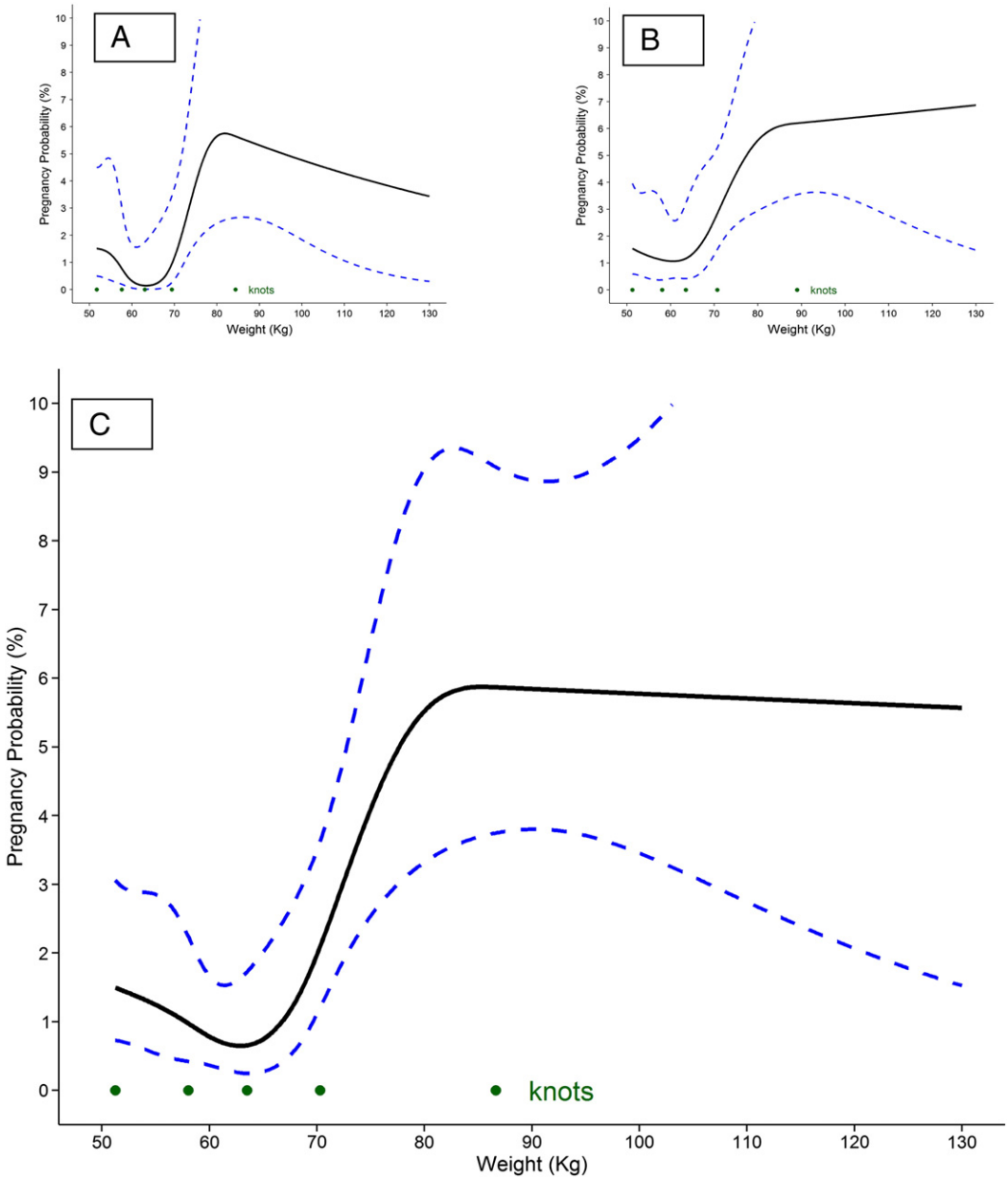

Fig. 3. Cubic spline logistic regression of pregnancy risk following LNG EC according to weight. Black line represents pregnancy rate with dotted lines representing the 95% CI. Knots are percentiles 10%, 30%, 50%, 70% and 90% of the weight distribution. (A) Creinin, 2006 (*N*=773). Association Wald test: p=.0626, linearity Wald: p=.151. (B) Glasier, 2010 (*N*=958). Association Wald test: p=.0199, linearity Wald test: p=.286. (C) Pooled analysis (*N*=1731). Association Wald test: p=.0003, linearity Wald test: p=.03.

LNG in women with higher body weights are unlikely to be the mechanism by which efficacy is reduced in these women.

The findings of these analyses have not been reported in previous LNG clinical trials, most likely because the women in the seminal international World Health Organization trials had substantially lower body weights; on average, women weighed about 10 kg less than in this pooled analyses and had an average BMI of 22 kg/m^2 [1,2]. Importantly, the pregnancy rates overall were very low in these studies, some with rates <1% [13,14], making detection of any effect more difficult. Additionally, the majority of the study populations came from non-Western settings.

The results of these analyses show that for women with higher body weights, particularly beyond 75 kg, LNG is less effective in preventing pregnancy. Decreased efficacy for these women may be an important safety issue, as overweight and obese women are at increased risk of several pregnancy complications, including gestational diabetes mellitus, hypertension, preeclampsia and cesarean delivery [15–18]. The most effective alternative strategy for EC is placement of a copper intrauterine device; however, insertion requires an intervention by a trained health provider. As most women will not have or desire this option, UPA may be considered, as the effect of BMI appears to

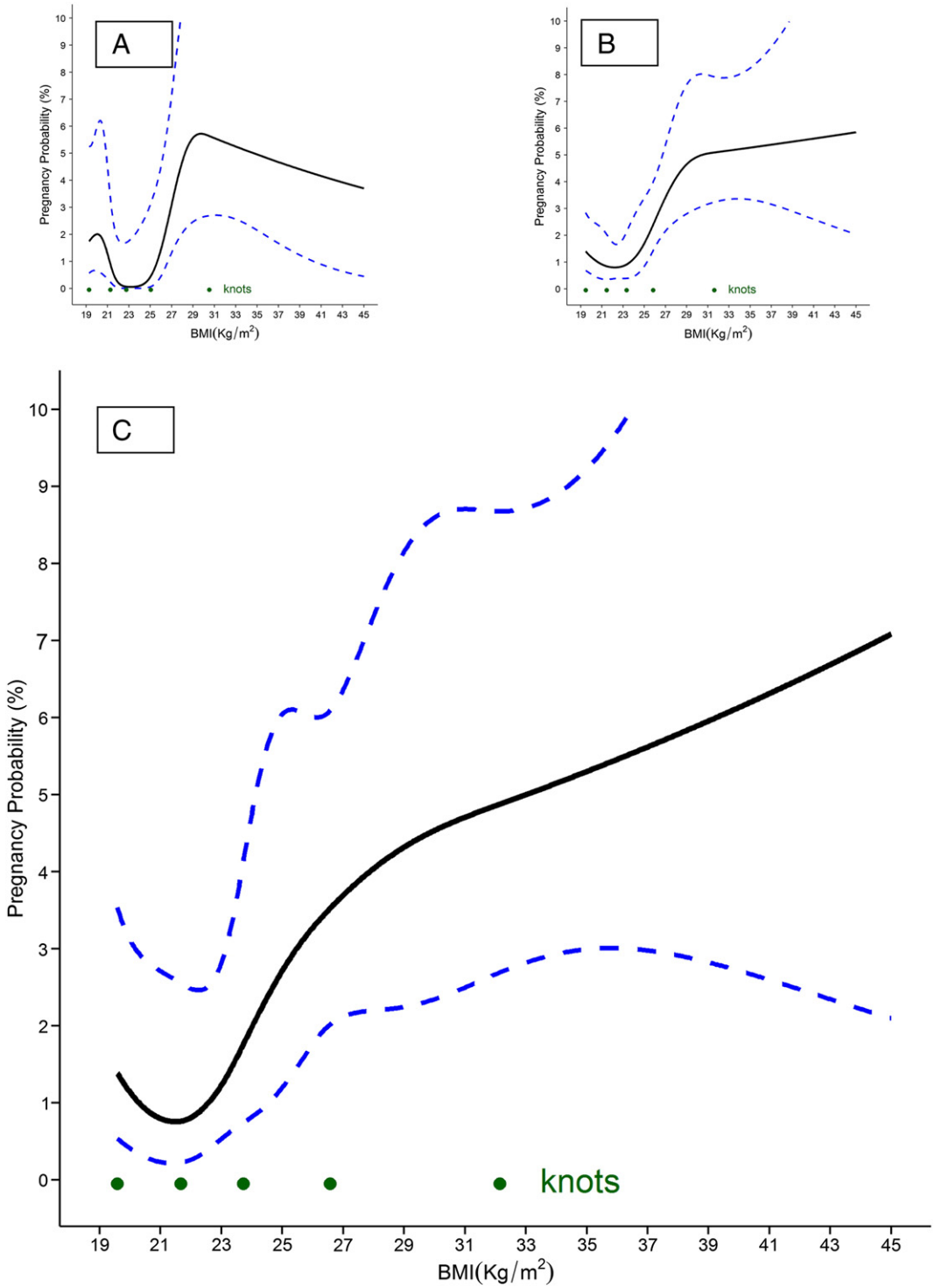

Fig. 4. Cubic spline logistic regression of pregnancy risk according to BMI. Black line represents pregnancy rate with dotted lines representing the 95% CI. Knots are percentiles 10%, 30%, 50%, 70% and 90% of the BMI distribution. (A) Creinin, 2006 (*N*=773). Association Wald test: p=.080, linearity Wald: p=.162. (B) Glasier, 2010 (*N*=958). Association Wald test: p=.055, linearity Wald test: p=.247. (C) Pooled analysis (*N*=1731). Association Wald test: p=.001, linearity Wald test: p=.050.

be less pronounced than with LNG in a previous meta-analysis [4], although confirmatory studies or analyses are not yet available.

Although the underlying mechanisms for decreasing efficacy are not fully understood, the negative effect of increasing body weight and BMI on LNG efficacy is striking.

Table 4
Observed pregnancy rate and proportion of the concerned studied population according to weight and BMI limits.

	Weight <75 kg	Weight >75 kg
BMI <25 kg/m^2	1.3% (14/1115) (95% CI=0.7%–2.1%); percent of population=64.4%	12.5% (1/8) (95% CI=0.3%–52.7%); percent of population=0.5%
BMI >25 kg/m^2	1.4% (4/276) (95% CI=0.4%–3.7%); percent of population=15.9%	5.7% (19/332) (95% CI=3.5%–8.8%); percent of population=19.2%
BMI >30 kg/m^2	0.0% (0/20) (95% CI=0.1%–24.9%); percent of population=1.2%	6.3% (14/222) (95% CI=3.4%–10.4%); percent of population=12.8%
BMI >35 kg/m^2	NC (no data); percent of population=0.0%	4.3% (4/93) (95% CI=1.2%–10.6%); percent of population=5.4%

Providing complete information about these results to providers and women is therefore of upmost importance, particularly in populations where women are increasingly overweight.

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