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Original Article

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Abstract

Objective: A pooled analysis of 2 randomized controlled trials (RCTs) suggested that increased bodyweight and body mass index (BMI) may be associated with a greater probability of pregnancy. To address this issue we investigated whether higher bodyweight and/or BMI negatively impacted the risk of pregnancy in women receiving LNG-EC (levonorgestrel-emergency contraception) after unprotected sexual intercourse in a pooled analysis of three large multinational RCTs conducted by the World Health Organization (WHO).

Methods: A pooled-analysis of 3 double-blind, multinational RCTs conducted by the WHO to investigate the efficacy of LNG-EC in the

general population. All analyses were done on the per-protocol set which included 5812 women who received LNG-EC within 72 hours following unprotected sexual intercourse. The analysis was based on logistic regression, with pregnancy as the outcome. BMI and weight were represented in the same model.

Results: A total of 56 pregnancies were available for analysis in the PPS. Increasing bodyweight and BMI were not correlated with an increased risk of pregnancy in the studied population. A limitation of this study is that despite the large study population in the pooled-analysis there were relatively small numbers of women in the high-BMI and high-bodyweight subgroups.

Conclusion: LNG-EC is effective for preventing pregnancy after unprotected intercourse or contraceptive failure and no evidence was found to support the hypothesis of a loss of EC efficacy in subjects with high BMI or bodyweight. Therefore, access to LNG-EC should not be limited only to women of lower bodyweight or BMI.

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ORIGINAL ARTICLE

Impact of bodyweight / body mass index on the effectiveness of emergency contraception with levonorgestrel: a pooled-analysis of three randomized controlled trials

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Key words: bodyweight, body mass, contraception failure, emergency contraception, levonorgestrel

[Short title: Emergency contraception with levonorgestrel]

Abstract

Objective: A pooled analysis of 2 randomized controlled trials (RCTs) suggested that increased bodyweight and body mass index (BMI) may be associated with a greater probability of pregnancy. To address this issue we investigated whether higher bodyweight and/or BMI negatively impacted the risk of pregnancy in women receiving LNG-EC (levonorgestrel-emergency contraception) after unprotected sexual intercourse in a pooled analysis of three large multinational RCTs conducted by the World health Organization (WHO).

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Results: A total of 56 pregnancies were available for analysis in the PPS. Increasing bodyweight and BMI were not correlated with an increased risk of pregnancy in the studied population. A limitation of this study is that despite the large study population in the pooled-analysis there were relatively small numbers of women in the high-BMI and high-bodyweight subgroups.

Conclusion: LNG-EC is effective for preventing pregnancy after unprotected intercourse or contraceptive failure and no evidence was found to support the hypothesis of a loss of EC efficacy in subjects with high BMI or bodyweight. Therefore, access to LNG-EC should not be limited only to women of lower bodyweight or BMI.

Introduction

Emergency contraception (EC), also known as post-coital contraception, refers to contraceptive methods that can be used to prevent pregnancy after unprotected or inadequately protected sexual intercourse. To be effective, EC should be used within a limited time frame, which depends on the method, but ranges from 72 to 120 hours after sexual intercourse¹.

During the last 15 years, following large multinational double-blind, randomized controlled trials (RCTs) conducted by the WHO, EC pills containing levonorgestrel (LNG-EC) have emerged as the most widely available and recommended method for oral EC²⁻⁵. Several studies have been conducted to establish the efficacy and safety of a standard regimen of LNG 1.5 mg (administered in two doses of 0.75 mg taken 12 hours apart or as a single-dose)³⁻⁵. To be effective, LNG-EC should be used as soon as possible after the unprotected sexual intercourse and within 72 hours. LNG-EC can inhibit or delay ovulation through an effect on follicular development⁶. However, when luteinizing hormone (LH) levels start to rise LNG cannot prevent ovulation and it has no effect post-ovulation⁷. LNG-EC cannot prevent implantation and has no negative impact on a pregnancy should it occur⁸.

Recently, the progesterone receptor modulator ulipristal acetate (UPA) has emerged as a novel oral method for EC which can be effective up to 120 hours after intercourse⁹. UPA-EC is still not as widely available as LNG. The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has recommended a change in classification status from prescription to non-prescription for the UPA containing emergency contraceptive, however it has not been approved by all EU countries as yet¹⁰. In a meta-analysis including data from two RCT single-blind trials UPA appeared more effective in preventing pregnancy (2 trials; RR 0.63) than LNG, but the difference did not achieve statistical significance ($P = 0.09$)^{9,11}. An influence of bodyweight and body mass index (BMI) on efficacy for both compounds was

reported by Glasier and co-authors; however, it was more pronounced for LNG-EC¹². Not surprisingly, it was found that the cycle day that the unprotected intercourse took place, as well as further acts of unprotected intercourse after EC were both related to an increased risk of pregnancy. Other variables such as age, time from unprotected intercourse to EC and history of previous pregnancy were not shown to contribute to the risk of pregnancy.

Overweight and obesity are increasing health problems worldwide. In many parts of the world, the problem is most pronounced among women of reproductive age. Based on the above-mentioned finding of an influence of bodyweight on the efficacy of EC pills, access to LNG-EC has been questioned in some countries. As a consequence, overweight women may have fewer options for EC and this is despite the fact that neither of the studies analyzed by Glasier and colleagues, or any other studies evaluating EC effectiveness, has been specifically designed to explore the effect of bodyweight on the effectiveness of EC¹². Since timely access to EC is recognized as an important component of a woman's reproductive health status and choices, it is crucial to further explore a possible effect of bodyweight and/or BMI on LNG-EC efficacy to ascertain whether there is a direct correlation to EC failure. To date only retrospective data analyses of clinical studies performed in the general population have been published. The more substantive the information base that we analyse the better our position will be to offer sound advice regarding EC to women with higher bodyweights / BMIs.

Thus, the aim of the present study was to examine whether the effectiveness LNG-EC was influenced by bodyweight and/or BMI based upon individual data derived from previously published, large, randomized, controlled trials in the general population conducted by the World Health Organization (WHO) Task Force on Postovulatory Methods for Fertility Regulation.

Methods

Data

Data were extracted from the levonorgestrel arms of three randomized, double-blind, clinical trials of EC conducted by the World Health Organization (WHO) Task Force on Postovulatory Methods for Fertility Regulation using a similar design³⁻⁵. In brief these trials were:

- A comparison with Yuzpe regimen (2 doses of ethinylestradiol 100 µg plus levonorgestrel 0.5 mg or *d,l* norgestrel 1.0 mg administered 12 hours apart) in which 1001 women (mean age 27.3 years) were allocated to receive LNG-EC administered as two doses of 0.75 mg taken 12 hours apart³.
- A comparison with mifepristone (10 mg single-dose) in which 1379 women were allocated to receive LNG-EC 1.5 mg as a single-dose and a further 1377 women two doses of LNG 0.75 mg taken 12 hours apart⁴. The mean age was 27 (range 14-52) years.
- A comparison of single-dose LNG-EC 1.5 mg (n=1512) with LNG-EC administered as two doses of 0.75 mg taken 12 hours apart (n=1510)⁵. The mean age was 26 years.

Statistical analysis and outcomes

All descriptions and analyses were performed on the per-protocol set (PPS) which comprised women who took the EC within the recommended 72-hour time period and who had available follow-up data. Treatment delay values (hours between unprotected intercourse and administration of EC) less than zero or exceeding 72 hours, in accordance with the approved use of LNG-EC pills (Product Information), were excluded from the PPS. Women with missing values regarding pregnancy outcome after the unprotected intercourse (yes or no) were also excluded. Subject characteristics were described in terms of mean and standard deviation (SD) for continuous variables, and absolute and relative category frequencies for categorical

variables. Non-pregnant and pregnant subjects were visualized on scatter plots of bodyweight versus body height. For descriptive purposes, BMI was categorized with cut points at 18, 25, 30, and 35 kg/m², and bodyweight with cut points at 55, 65, 75, and 85 kg. Empirical relative frequencies of pregnancy were expressed for all existing combinations of these categories, in percentage form with exact binomial 95% confidence intervals (CI). Subjects whose unprotected intercourse had occurred during the fertile window (beginning 5 days before and ending one day after expected ovulation) were assigned conception probability values following the Trussell model¹³. For intercourse days outside this range, but within days -28 to +14 (inclusive), the probability was set to zero, otherwise to missing.

Analysis was based on logistic regression using the statistical software Stata (StataCorp), with pregnancy as the outcome. BMI and bodyweight were both represented in the same model as continuous variables. Quadratic and cubic variants, as well as interaction terms, were used to enable the model to follow curvatures of the outcome function. Other explanatory variables were included unless observed to have a neutral behavior, with quadratic or cubic terms if this improved model fit. Effects were expressed as odds ratios (OR) and 95% CIs. Model fit was assessed using the Hosmer–Lemeshow test and by visual comparison of observed and fitted probabilities across BMI and weight groups. *P* values less than 0.05 were considered to indicate statistical significance.

Results

The number of unique, single-subject records remaining after data cleaning was 6779, with 72 pregnancies (Figure 1). A total of 916 records were eliminated; in the majority cases the patient had received EC after the allowed 72-hour time period, but before 120 hours which was permitted in some centres. Thus, 5863 subjects (59 pregnancies) were included in the PPS for the meta-analysis, with a pregnancy rate of 1%.

Subject characteristics are described in Table 1. On average, subjects were relatively young, with BMI in the healthy range, and treatment delay exceeding one day; almost two-thirds had been pregnant before. A special subgroup of women ($N=60$) who were exceptionally short for their weight was identified by plotting bodyweight against body height; the phenomenon occurred almost exclusively in 3 of 9 study groups in Nigeria (Africa). Of note, these subjects represented 1% of the sample, but 4 of 59 (6.8%) pregnancies. In this anthropological subset the relative frequency of pregnancy was 6.7% compared to 0.9% in the remainder of the total sample. The findings were also in sharp contrast to the full African data, where pregnancy risk was generally the lowest (0.5% including the contribution of these subjects) compared to other geographic regions.

The observed unadjusted relationship between BMI, bodyweight and pregnancy is shown in Figure 2. There is an isolated hotspot at around BMI 32.5 kg/m^2 and bodyweight between 55 and 74 kg. Also, there is a marginal ramp coinciding with a single pregnancy in subjects who are at the high end of the BMI and bodyweight range. Both these peaks are fully explained by the subgroup found within the 3 above-mentioned Nigerian study sites (they disappear from the heat map if these subjects are excluded). The probability plane being highly and irregularly curved indicated that a logistic regression model would require higher order terms for a plausible fit. It is also evident that the effect of BMI is heterogeneous across levels of bodyweight, and *vice versa*, making it necessary to use interaction terms between the two.

A logistic regression model with squared and cubed BMI and bodyweight terms and interactions was fitted and found to be consistent with the data. Other explanatory variables included continent, treatment delay, expected probability of pregnancy, and age. The fit was sufficient according to the Hosmer–Lemeshow test ($p = 0.236$), and a heat map of fitted probabilities indicated that both the isolated hot spot and the top-edge marginal ramp were retained. The

marginal effects of BMI, bodyweight, treatment delay, expected probability of pregnancy, and age were selectively significant in a location-dependent manner.

Effects of BMI and bodyweight

The estimated marginal effects associated with a unit increase in BMI from a defined reference level were mostly very close to neutral or had very wide CIs. One group of technically significant effects was located at reference BMI in the range 24 to 30 kg/m², and bodyweight between 50 and 65 kg, with an odds ratio of up to 1.47 (95% CI: 1.13 to 1.92) and the effect exceeding a narrow range of equivalence (OR between 1/1.1 and 1.1). A single additional, very weakly significant effect (OR 2.18 [95% CI: 1.03 to 4.62]) appeared at BMI 44 kg/m² and bodyweight 80 kg, consistent with the top-edge ramp.

The estimated effects of bodyweight were similar to those of BMI in terms of size of departure from neutrality and patterns of uncertainty. Statistically significant effects were located in the BMI range 26 to 30 kg/m², and bodyweight between 65 and 70 kg. At higher bodyweights relative to BMI, the risk of pregnancy decreased (Table 2). This corresponds to the downward slope from the top of the isolated hot spot towards greater bodyweights with BMI remaining constant. Marginal effects were almost exclusively inside a wide range of equivalence (OR between 1/1.25 and 1.25) or exceeded it primarily towards the negative direction in the area defined by the BMI range 18 to 24 kg/m², and weight range 45 to 60 kg. Table 2 illustrates how these effects manifest across the outcome space as a function of BMI and body weight, relative to a reference point of 22.5 kg/m² and 60 kg, i.e., women with close to the average body characteristics in the current sample.

Effects of other factors

The odds of pregnancy were significantly lower in Africa than in the reference category of non-African, non-Asian regions (OR = 0.26). There was no significant difference between Asia and

the non-African, non-Asian population. Across the observed age range, the probability of pregnancy initially increased, peaked at around 30 years, and then declined. The rate of the increase was significant in the range 15 to 25 years, and that of the decline, from 45 years and beyond.

Up to 48 hours delay in providing EC was not observed to influence the chances of pregnancy. However, a progressively significant rise in the risk of pregnancy occurred when the delay in giving EC reached 54 hours, a point beyond which further delay meant a loss of EC efficacy.

Across the observed range, greater expected conception probability (Trussell method) was generally associated with greater odds of pregnancy¹³. The rate of this increase was initially highest, gradually declined, and leveled out at about 20%. Higher levels of estimation uncertainty in the low expected probability range meant that the marginal effects did not reach significant levels except at 12% as the reference location.

Discussion

The pooled data from the 3 clinical trials in this meta-analysis including 5812 women with 56 registered cases of pregnancy following the use of LNG-EC (with a treatment delay of not more than 72 hours) showed a high overall contraceptive effectiveness with a pregnancy risk between 0.57% and 1.8%. The pregnancy rate in the whole population was 1%. High BMI or bodyweight were not substantiated as factors increasing the risk of pregnancy. All adjusted marginal effects of BMI that were technically significant are explained by the presence of a single anthropological subgroup of women who were exceptionally short for their weight; this group is atypical to such an extent that any generalization of these seemingly positive findings beyond the limits of the study sample would be prohibitively difficult. Increased bodyweight was not observed to be significantly associated with greater probabilities of pregnancy; its significant (pseudo)protective effects can be explained as artifacts, again as a result of the cluster of

pregnancies described above. The strength of support provided by this evidence for a hypothesis of loss of EC efficacy in high-BMI subjects (as proposed in a previous meta-analysis by Glasier *et al.*, 2011) is zero to extremely limited¹¹.

There are no data indicating that obesity would reduce the contraceptive efficacy of combined hormonal contraceptives¹⁴. The previous meta-analysis by Glasier and colleagues involving two studies by Creinin *et al.* and Glasier *et al.* reported a significant influence of bodyweight and BMI on the efficacy of EC pills, and this was slightly more pronounced for LNG-EC compared with UPA-EC^{9,11,12}. Several possible factors could contribute to the different findings. These factors alone might not cause significant change in the overall picture, but could reinforce or weaken a tendency. Firstly, the treatment delay may be different in the two meta-analyses (120 versus 72 hours). There are no details available on the fraction of women who received LNG-EC beyond the labelled 72 hours' time frame in the meta-analysis by Glasier and colleagues to assess whether this affected the risk of pregnancy. Secondly, in one of the studies included in the efficacy evaluation of the pooled data the women themselves estimated their weight which was not objectively controlled¹². This methodology may be problematic as the 'efficacy evaluable' population criteria are not identical in the two studies. Thirdly, the use of the analyzed populations (evaluability according to treatment delay or other criteria) seems to be inconsistent within the key publications^{9,11}. Noticeably, the studies included in the present analysis contained data from patients who had only one act of unprotected intercourse before taking LNG-EC in contrast to the criteria in the studies included in the meta-analysis by Glasier and colleagues¹¹.

The findings regarding the effects of secondary explanatory factors are plausible and consistent with current knowledge, indicating the existence of an age range within which fecundity reaches a peak, the importance of timely post-coital intervention, and an association between calculated

baseline probability of pregnancy and observed frequency of conception. This is also consistent with the mechanisms of action of LNG-EC.

The decision to include both BMI and bodyweight in the current model seemingly contrasts with usual practice of avoiding correlated covariates. The conceptual basis for including both relates to the fact that high bodyweight can be the result of accumulated body fat (i.e. overweight), but may also be explained by a generally big body with a healthy tissue composition. High BMI can also result from high body fat, but will also be found in tall people (or very muscular persons) with significantly less body fat than their BMI would suggest. Analyzing either variable separately will thus yield compound effects of body size and fat content. However, when analyzing the effect of bodyweight with BMI held constant, the observed effect will be much closer to that of body size (overall pharmacokinetic distribution space) alone; and when analyzing the effect of BMI with bodyweight held constant, the observed effect will better represent that of body adipose tissue content or changes in lipid-to-water ratio (important pharmacokinetic consequences for lipophilic substances). If there is a loss of efficacy resulting from either of these two mechanisms, the current model will be more sensitive to determine this association since both BMI and bodyweight are used as exploratory variables. These general considerations for variable inclusion are further corroborated, in the present case, by prominent effect heterogeneity phenomena between BMI and bodyweight.

Limitations

A limitation of the current analysis is that high-BMI and high-bodyweight ranges were relatively poorly populated in the analyzed dataset, as might be expected for a study which did not specifically recruit to ensure sufficient coverage close to those higher distribution extremes.

Nevertheless, we believe that the present analysis delivers an important general message. *Post hoc* analyses of historic data to address safety or efficacy concerns are common, even when they

were not originally designed to specifically address these outcomes. Another limitation of this type of analysis is dependency on self-reporting of some data such as time interval after intercourse, cycle length, and the number of times intercourse took place before and after treatment. Because of the relatively small number of pregnancies (n=56), caution has to be shown when interpreting the results. For example, it is possible with our current data to fit a model that predicts significantly growing pregnancy odds with increasing BMI, and that model will pass a common goodness-of-fit test. However, the BMI effect in that model will be highly dubious, and is fully explained by three pregnancy observations, all in a single anthropological subgroup.

Conclusion

Based on the results of this analysis involving 5812 women, no evidence was found supporting the hypothesis of loss of EC efficacy in subjects with high BMI or bodyweight. Therefore, as has recently been concluded by the EMA, based on the data presented here, access to LNG-EC should not be limited to women of lower bodyweight or BMI (EMA Assessment Report 2014)¹⁵. Any increase in EC efficacy that is achieved is beneficial to the great number of women who have already had unprotected intercourse, offering them a second chance to prevent an unintended pregnancy.

Transparency

Declaration of funding:

Statistical analyses was funded by Gedeon Richter. The original 3 studies were conducted by the World Health Organization (WHO) Task Force on Postovulatory Methods for Fertility, and were funded by the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, WHO. Gedeon Richter Plc

donated LNG tablets for these studies, but had no role in the design of the study, data collection, data analysis, data interpretation or the final meta-analysis comprising this publication.

Declaration of financial/other interests:

HvH was responsible for the trials as an employee of the WHO. KGD participated as a PI in two of the trials and was as a member of the WHO task force on post ovulatory methods for fertility regulation which designed and conducted the trials. The Authors have no other relevant financial relationships to disclose. CMRO Peer Reviewers on this manuscript have no relevant financial relationships to disclose.

Author contributions:

LK contributed to the study protocol development, statistical analysis and drafting of the report. HvH was responsible for organizing the original three RCTs while employed by the WHO and contributed to the drafting of the report. KGD participated as a member of the WHO task force on post ovulatory methods for fertility regulation in the design and conduct of all included trials and in two of the RCTs as a principal investigator. She contributed to the study conception and drafting of the report. Gedeon Richter had no role in the design of the study, data collection, data analysis, data interpretation or the final meta-analysis comprising this publication.

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Figure legends.

Figure 1 Subject flow profile.

The per-protocol (PP) population using the product within the 0-72 hour time frame was 5863 (59 pregnant). PP population using the product within the 0-72 hour time frame and data about BMI status not missing: 5859 (59 pregnant). PP population using the product within the 0-72 hour time frame and all pre-defined variables in the analysis reported: 5812 (56 pregnant).

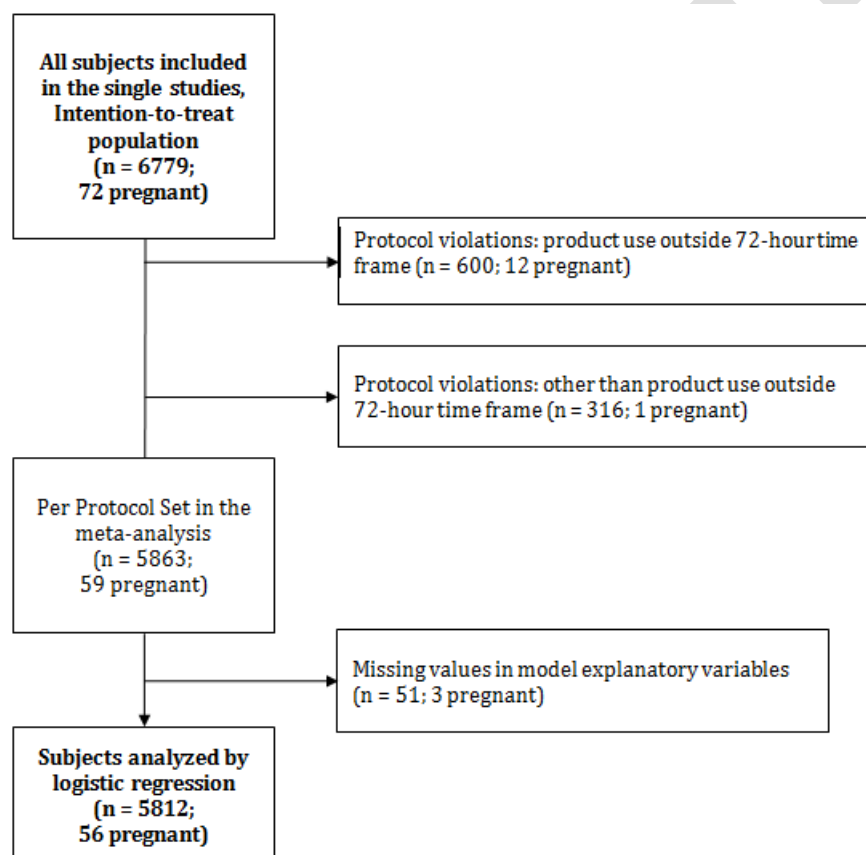


Figure 2. Empirical probability (%) heat map of pregnancy in subgroups defined by BMI and bodyweight. Figures in parentheses indicate numerators and denominators from which percentages were derived; those in square brackets indicate 95% confidence intervals for the percentage.

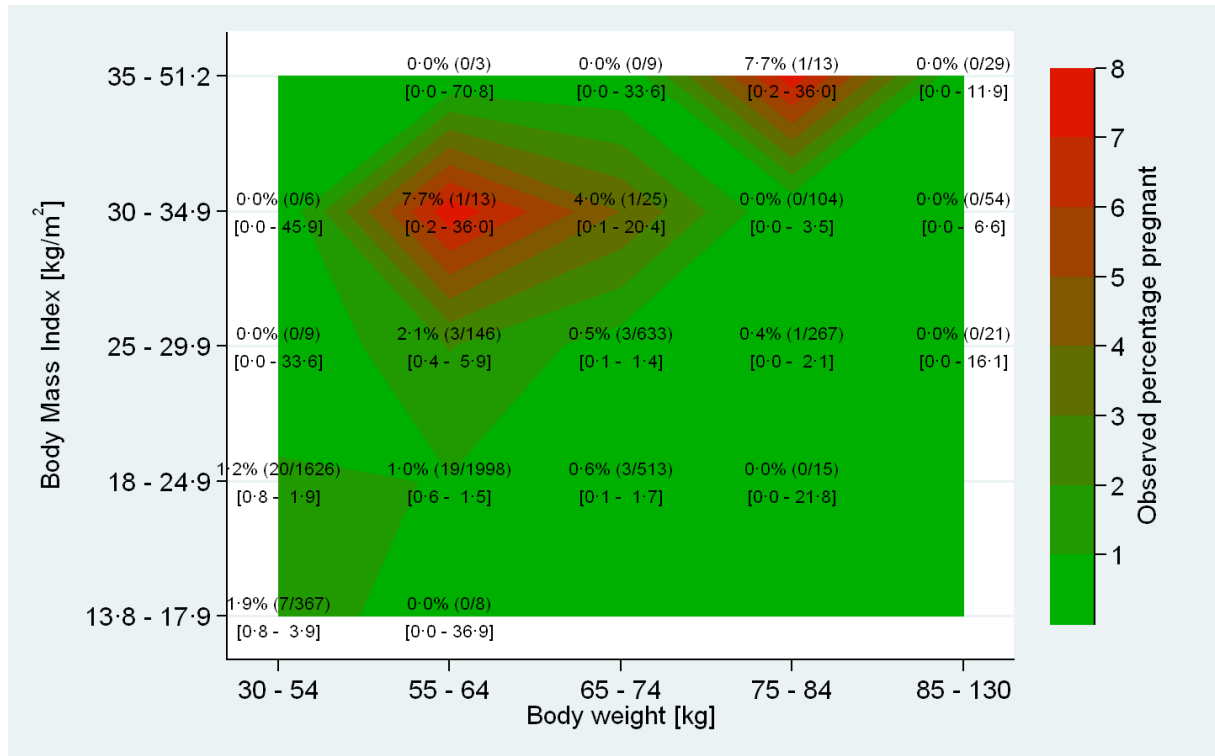


Table 1 Characteristics of subjects and crude pregnancy rates

Characteristic	N	Mean (SD) n (%)	or Crude pregnancy risk (%) [95% CI]
<i>Continuous variables</i>			
Age	586 2	27.0 (6.5)	N/A
Bodyweight [kg]	585 9	59.5 (10.3)	N/A
Body height [cm]	586 0	162.6 (6.7)	N/A
Body Mass Index [kg/m ²]	585 9	22.5 (3.9)	N/A
Treatment delay [h]	586 3	29.9 (18.7)	N/A
Expected probability of pregnancy [%]	581 6	9.1 (10.9)	N/A
Length of menstrual cycle [d]	586 3	28.8 (2.4)	N/A
<i>Categorical variables</i>			
Pregnant	586 3		
no		5804 (99.0%)	N/A
yes		59 (1.0%)	N/A
Body Mass Index [kg/m²] group	585 9		
13.84 - 18.00		406 (6.9%)	1.7 [0.7 to 3.5]
18.03 - 25.00		4158 (71.0%)	1.0 [0.7 to 1.4]

25.01 - 29.93	1039 (17.7%)	0.6 [0.2 to 1.3]
30.02 - 34.89	202 (3.4%)	1.0 [0.1 to 3.5]
35.00 - 51.20	54 (0.9%)	1.9 [0.0 to 9.9]
Bodyweight [kg] group	585 9	
30 - 54	2008 (34.3%)	1.3 [0.9 to 2.0]
55 - 64	2168 (37.0%)	1.1 [0.7 to 1.6]
65 - 74	1180 (20.1%)	0.6 [0.2 to 1.2]
75 - 84	399 (6.8%)	0.5 [0.1 to 1.8]
85 - 130	104 (1.8%)	0.0 [0.0 to 3.5]
Continent	586 3	
Am/Aus/Eur	1255 (21.4%)	1.0 [0.5 to 1.7]
Africa	2683 (45.8%)	0.5 [0.3 to 0.9]
Asia	1925 (32.8%)	1.7 [1.2 to 2.4]
Treatment group	586 3	
Single 1.50mg	2461 (42.0%)	0.9 [0.6 to 1.4]
Double 0.75mg	3402 (58.0%)	1.1 [0.8 to 1.5]
Further intercourse* #	585 6	
no	3806 (65.0%)	0.9 [0.6 to 1.3]
yes	2050 (35.0%)	1.2 [0.8 to 1.7]
Number of further acts of intercourse* #	204 9	

1	699 (34.1%)	1.3 [0.6 to 2.4]
2	627 (30.6%)	1.1 [0.5 to 2.3]
>2	723 (35.3%)	1.0 [0.4 to 2.0]
<hr/>		
Previous pregnancies	586	
	3	
none	2110 (36.0%)	0.7 [0.4 to 1.2]
1 or more	3753 (64.0%)	1.2 [0.9 to 1.6]
<hr/>		

Confidence intervals (CI) for rate point estimates of 0.0% are one-sided 97.5% intervals.

N = number of non-missing observations, * Refers to the current menstrual cycle,

Protected intercourse. Women were advised not to have unprotected sex, and were given condoms. Participants were asked in the single studies to keep a diary of side-effects in the week after the treatment, and to record when a condom was used.

Table 2 Odds ratios [95% confidence intervals] for pregnancy at selected levels of BMI and bodyweight relative to the odds at the reference point of 22.5 kg/m² and 60 kg. N/A indicates locations of insufficient sample coverage for effect estimation

BMI\BW	40	45	50	55	60	65	70	75	80
18	2.15 [0.41 - 11.3]	1.51 [0.63 - 3.59]	1.83 [0.90 - 3.74]	2.62 [0.85 - 8.10]	2.98 [0.39 - 22.6]	N/A	N/A	N/A	N/A
20	N/A	1.80 [0.54 - 5.99]	1.32 [0.73 - 2.42]	1.26 [0.84 - 1.89]	1.19 [0.55 - 2.58]	0.86 [0.11 - 6.67]	N/A	N/A	N/A
22.5	N/A	N/A	2.16 [0.81 - 5.75]	1.42 [0.88 - 2.28]	reference point	0.67 [0.35 - 1.29]	0.38 [0.046 - 3.16]	N/A	N/A
25	N/A	N/A	5.17 [1.03 - 25.9]	3.10 [1.17 - 8.17]	1.74 [1.00 - 3.05]	0.94 [0.55 - 1.60]	0.50 [0.19 - 1.31]	N/A	N/A
30	N/A	N/A	N/A	13.7 [2.14 - 87.2]	10.9 [2.06 - 57.4]	4.53 [0.91 - 22.6]	1.32 [0.23 - 7.41]	0.35 [0.030 - 4.09]	N/A
40	N/A	N/A	N/A	N/A	N/A	N/A	12.5 [0.12 - 1339]	1.02 [0.0022 - 475]	0.011 [1.0×10 ⁻⁷ - 1072]
50	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	483 [1.69 - 138500]