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Emergency contraception: Summary

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Office of Evidence Based Practice – Specific Care Question: Emergency Contraception for the Adolescent Patient

Specific Care Questions:

In the adolescent female who presents for emergency contraception (EC), does body mass index (BMI) influence choice of recommended oral EC?

In the adolescent female who presents for EC does the number of hours from unprotected sexual intercourse influence the choice of recommended oral EC?

Question Originator:

Melissa Miller, MD

Plain Language Summary from The Office of Evidence Based Practice:

Since the last literature synopsis on the efficacy of levonogestrel (LNG, Plan B) and ulipristal (ULI) for EC, two papers are added to the summary. The first is (Black et al., 2015) the consensus statement of the Society of Obstetricians and Gynaecologists of Canada (SOGC), and the second is (Kapp et al., 2015), a secondary analysis of the Creinin et al. (2006) and Glasier et al. (2010) papers.

In the evaluation of the body of evidence on this question, it is apparent that two papers (Creinin et al., 2006; Glasier et al., 2010) form the core of the evidence. These studies will be referred to as the core papers hereafter. Papers published since the initial literature review on 10/2014 are secondary analyses of the data from the core papers. Other secondary sources convey that ULI is believed to be more effective than LNG (U.S. Department of Health & Human Services, 2014).

Body Mass Index

Based on very low quality evidence, for women who have a BMI of $> 25 \text{ mg/m}^2$, ULI may have greater efficacy to prevent pregnancy. The recommendation may change when higher-quality evidence becomes available. Although the core studies have low risk of bias, the secondary analysis is based on an outcome that the core papers did not intend for the original research. Further research (if performed) that compares the efficacy of different ECs and stratifies randomization by BMI is likely to have an important influence on our confidence in the estimate of the effect and is likely to change the estimate of the effect.

Summary of guidelines

SOGC (Black et al., 2015) states the use of EC should be available to all women seeking it, without regard to BMI, and for women with a BMI $> 25 \text{ kg/m}^2$ ULI should be the first choice, if available and affordable.

American Academy of Pediatrics (AAP) (Braverman et al. 2014) states ULI may be used over LNG in adolescents with a body weight of > 165 pounds based on the Glasier (2010) study, highlighted below.

The Centers for Disease Control and Prevention (CDC, 2013), the European Medicines Agency (EU, 2014), and the Clinical Effectiveness Unit of the Royal College Faculty of Sexual and Reproductive Healthcare (FSRH, 2012) agree that there is not enough evidence to use body mass index (BMI reported in kg/m^2) as a criteria when choosing between levonogestrel and



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ulipristal for EC.

Primary research papers

Creinin et al. (2006) study was a double-blinded non-inferiority trial. The goal of this trial was to show that ULI was as efficacious as LNG for EC (see Figure 2). This goal was met. Glasier, et al. (2010) study was also a double-blinded non-inferiority trial. It compared ULI versus LNG up to 120 hours after unprotected sexual intercourse. The goal was to show that ULI was as efficacious as LNG for EC (see Figure 2). A secondary data meta-analysis is reported in this paper. The authors combined the data from Creinin et al. (2006) with data from the current study and affirmed with a larger study population that ULI is not inferior to LNG as an EC ($OR = 0.75$, 95% CI 0.45, 1.24). The BMI comparison was not reported in the non-inferiority studies.

Secondary research papers

Glasier et al., (2011) performed a secondary data analysis from the core randomized controlled trials where risk factors of EC failure were identified. Three factors were found to have a statistically significant effect on the risk of pregnancy: (a) BMI (kg/m^2), (b) conception probability (defined as the period within five days prior to ovulation to 1 day after ovulation), and (c) further sexual intercourse. However, when participants were stratified by body weight (a) normal or underweight ($BMI < 25 \text{ kg}/\text{m}^2$), (b) overweight ($BMI \geq 25$ and $< 30 \text{ kg}/\text{m}^2$), and (c) obese ($BMI \geq 30 \text{ kg}/\text{m}^2$) statistically significant differences were not found between body weight groups. However, for the total effect in this analysis, ULI performed significantly better than LNG (see Figure 3).

Kapp, et al. (2015) performed a secondary data analysis from the core randomized control trials and reported on efficacy of LNG with the comparison of $BMI < 25 \text{ kg}/\text{m}^2$ versus $BMI > 25 \text{ kg}/\text{m}^2$. The authors report that LNG was significantly more efficacious in preventing pregnancy in women with a $BMI < 25 \text{ kg}/\text{m}^2$ ($OR = 0.35$, 95% CI 0.18, 0.67) than those with a $BMI > 25 \text{ kg}/\text{m}^2$ (see Figure 5).

Although the core studies have low risk of bias, the secondary research papers Glasier et al. (2011) and Kapp et al. (2015) have biases. The evidence is downgraded for four reasons:

1. The secondary analyses address BMI and EC success or failure in women with $BMI > 25 \text{ kg}/\text{m}^2$. A sample size calculation is not provided to perform this analysis.
2. There were a low number of treatment failure events (i.e., pregnancy) in the overweight and obese groups. A low number of events decreases the precision of the findings.
3. It is difficult to repeat the meta-analyses for confirmation. In the core reports, the number of subjects in the efficacy evaluable populations is 3448 and in the Glasier et al. (2011), secondary analysis the number of subjects is 3445. In addition, the numbers of treatment failures vary among the reports. The core studies report a sum of 57 treatment failures, while Glasier et al. (2011) reports 60 treatment failures, a difference of 5%.



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4. Note that the secondary research papers (Glasier, 2011;Kapp, 2015) are prepared by the primary study sponsor (HRA Pharma), and reporting bias is unclear.

Time to Treatment with ECs

Based on very low quality evidence, the Office of Evidence Based Practice recommends to use either LNG or ULI within the first 72 hours after unprotected sexual intercourse. Based on very low quality evidence the Office of Evidence Based Practice makes a conditional recommendation to use ULI for EC in the patient who presents between > 72 and < 120 hours after unprotected sexual intercourse.

Since the last literature synopsis was performed in October 2014 on the efficacy of levonogestrel (LNG, Plan B) and ulipristal (ULI, Ella) for EC, no new research was identified that addressed the time to treatment with ECs. The CDC (2013) states that ECs should be taken as soon as possible within five days of unprotected sexual intercourse, and that ULI and LNG have similar effectiveness when taken within three days of unprotected coitus. The CDC (2013) continues to state that ULI has been shown to be more effective three to five days after unprotected sexual intercourse. The AAP Policy Statement concurs with the CDC (2013) findings and states that ULI may have greater effectiveness at the end of the five day window (Braverman et al., 2014). The SOGC guideline (Black et al., 2015) also agrees with the CDC's (2013) statement.

For the “time to treatment with ECs” question, the evidence is found to be very low quality. Although the methods of the included studies are strong (see Figure 3), the evidence is downgraded for two reasons:

1. There is low number of events in the treatment groups. As seen in Figure 4, for the subgroups at 73-96 hours and 97-120 hours, there were a total of three pregnancies reported (low number of events decreases the precision of the findings).
2. The assessment of reporting bias is unclear; Glasier et al., (2010), there is high level of involvement of the study sponsor (HRA Pharma),

Overall, there was no difference in treatment failure (pregnancy) between the group treated with ULI and the group treated with LNG, $OR = 0.63$, 95% CI [0.37, 1.07], (see Figure 4). The sub-group analysis for time to treatment indicates that for time to treatment of 0-24 hours and 25-48 hours, there is no difference in EC failure between the two medications. For 49-72 hours to treatment, ULI has significantly less treatment failure, $OR = 0.36$, 95% CI [0.13, 0.99]. For times to treatment > 72 hours, data from ULI is unavailable (see Figure 4).

EBP Scholar’s Responsible for Analyzing the Literature:

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Search Strategy and Results:

Ovid Search Strategy: Levonogestrel/[Administration & Dosage, Adverse Effects, Contraindications, Pharmacokinetics, Pharmacology, Therapeutic Use, Standards] AND ulipristal AND (Body Mass Index/ OR Obesity/]

PubMed October 2014

Search Strategy: ("Levonorgestrel"[Mesh] OR levonorgestrel OR lgn OR "plan b") AND ("ulipristal acetate"[Supplementary Concept] OR "ulipristal"[Supplementary Concept] OR ulipristal OR CDB-2914 OR upa OR ella) AND (bmi OR "body mass index" OR "Body Mass Index"[Mesh] OR obes* OR overweight OR "Obesity"[Mesh] OR "Overweight"[Mesh] OR bodyweight)

Filters: English, published within the last 5 years

PubMed 2014 – February 2016

("Contraception, Postcoital"[Mesh] OR "Contraceptives, Postcoital"[Mesh] OR ((contracept* OR "birth control") AND (postcoital OR emergency)) OR "Levonorgestrel"[Mesh] OR levonorgestrel OR lgn OR "plan b" OR "ulipristal acetate"[Supplementary Concept] OR "ulipristal"[Supplementary Concept] OR ulipristal OR CDB-2914 OR upa OR ella) AND (bmi OR "body mass index" OR "Body Mass Index"[Mesh] OR obes* OR overweight OR "Obesity"[Mesh] OR "Overweight"[Mesh] OR bodyweight OR "body weight") **AND** ((systematic[*sb*] OR Meta-Analysis[*ptyp*] OR Randomized Controlled Trial[*ptyp*] OR "Cohort Studies"[Mesh]) AND ("2014/07/01"[*PDat*] : "3000/12/31"[*PDat*] AND English[*lang*])

TRIP database, Google Scholar, National Guidelines Clearinghouse, Dynamed, UptoDate, and Clinicaltrials.gov Feb 2016 using the keywords ulipristal, levonorgestrel, BMI, overweight, and obes*.

Ovid February 2016 (Contraeption, Postcoital/ or Contraceptives, Postcoital/ or ((contracept*.mp. or birth control.mp.) and (emergency.mp. or postcoital.mp.)) or Levonorgestrel/[Administragion & Dosage, Adverse Effects, Contraindications, Pharmacokinetics, Pharmacology, Standards, Therapeutic Use] or levonogestrel.mp. or lgn.mp. or plan b.mp. or ulipristal.mp. or upa.mp. or ella.mp.) and (Body Mass Index/ or body mass index.mp. or bmi.mp. or Body Weight/ or body weight.mp. or bodyweight.mp. or Obesity/ or obes*.mp. or Overweight/ or overweight.mp.)

The literature searches were repeated February 25 2016.

Studies included in this review:

Glasier et al., 2011

Glasier et al., 2010

Creinin et al., 2006



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Kapp et al., 2015

Guidelines and Evidence Reports included in this review:

Black et al., 2015

CDC, 2013

EU, 2014

FSRH, 2012

Method Used for Appraisal and Synthesis:

To answer the questions, (1) does BMI play a role when choosing EC and (2) does time from unprotected sexual intercourse play a role when choosing EC, OVID, PubMed and the TRIP database, Google Scholar, National Guidelines Clearinghouse, DynaMed, UptoDate and Clinicaltrials.gov were searched. Searches were performed by a medical librarian and search strategies are available. Twenty-four articles were identified, and five were chosen for this review. There were two major reasons for excluding articles (a) they were narrative reviews, and (b) they did not answer the questions. The included articles are Creinin et al. (2006); Glasier et al. (2011); Glasier et al. (2010); Kapp et al. (2015) The included guidelines and evidence reports are ACOG, (2010); FSRH, (2012); CDC, (2013); Black et al. (2015).

After studies were selected for review they were verified by the Evidence Based Practice Scholars (EBPS) at Children’s Mercy, Kansas City. The EBPS, nursing and allied health professionals, who are trained to use the Cochrane Collaborative computer program, Review Manager (RevMan 5.3), collected the following information from the selected studies:

- Article identification information (citation)
- Study characteristics (participant description, treatment (medication, dose, frequency), control, primary and secondary outcomes)
- Assessment of potential biases – Primary research studies were assessed for selection, performance, detection, attrition, and reporting biases.
- Data tables were created to report the results for the primary and secondary outcomes.

The studies that were not RCTs were assessed for the following:

- The chance of finding significance when multiple statistical tests are performed on the same data
- Ability to repeat the meta-analysis
- How potential confounding factors, such as inclusion and exclusion criteria and number of subjects who were exempt from the analysis

The work of the EBPS was independently validated by a member of the Office of Evidence Based Practice (NHA). If data for



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more than one study was available for the primary or secondary outcomes, estimate of effects were calculated as odds ratios (OR), with 95% confidence intervals (CIs). We did not contact trial authors for missing data. Three EBPS read the selected guidelines and scored them using the AGREE II tool (Brouwers et al., 2010). Scores were collated by a member of the Office of Evidence Based Practice (NHA).

Updated 8/27/2014, 8/28/2014 9/5/2014, 9/18/2014 3/21/2016, 2/16/2016

Table 1

Methods and Risk of Biases Assessments

Creinin 2006

Methods	RCT, double-blinded non inferiority trial
Participants	<p>Setting: a consortium of family practice clinics in the Los Angeles, CA area and five university based clinical research centers</p> <p>Randomized: 1672 women age 18+ seeking emergency contraception within 72 hours of unprotected intercourse</p> <p>Treatment group (CDB-2914): N=832</p> <p>Control group (levonorgestrel): N=840</p> <p>Completed: intent-to-treat population: 1549 (subgroups, broken down into time after unprotected intercourse: 0-24 hours, 24-48 hours, 48-72 hours)</p> <p>Treatment group (CDB-2914): N=775 (subgroups N= 273, 268, 234 depending upon elapsed time after intercourse)</p> <p>Control group (levonorgestrel) N=774 (subgroups N=263, 298, 213 depending upon elapsed time after intercourse)</p> <p>Inclusion Criteria: Healthy women age 18+ not using hormonal contraception who requested emergency contraception within 72hours after unprotected intercourse, who had a recent history of regular menstrual cycles and at least one normal menstrual cycle after delivery, abortion, or discontinuation of hormonal contraceptive.</p> <p>Exclusion Criteria: women who were pregnant or breastfeeding at time of screening or within 2 months before screening, using an intrauterine device or sterilization as a contraceptive method, uncertain about date of LMP, nausea or vomiting at time of screening or 2 weeks prior to screening, using oral glucocorticosteroid replacement therapy, or currently enrolled in another investigational trial.</p> <p>Power analysis: done, study goal was to enroll 770 subjects in each group. Numbers were increased</p>



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to 811 to allow for anticipated participants lost to follow-up.

Interventions

Treatment group: 50mg CDB-2914 + placebo 12 hours later
Control group: 0.75 levonorgestrel x 2, taken 12 hours apart

Outcomes

Occurrence of pregnancy after taking medication (data for 0-24 hours after intercourse, 24-48 hours, 48-72 hours) adverse effects, menstrual cycle length after treatment

Notes

"Final model retained site and body mass index as covariates", no information on BMI is listed in this article.

Risk of Bias Table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	RCT
Allocation concealment (selection bias)	Low risk	Study/control drug was supplied in sequentially numbered sealed packages containing two opaque capsules, packages were identical
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel were both blinded to study/control drug. Provisions made to packaging to ensure that if blinding was broken that tampering would be evident.
Blinding of outcome assessment (detection bias)	Unclear risk	Patients knew after study if they were pregnant or not, outcome data for adverse effects and cycle length were given in percentages, not actual numbers
Incomplete outcome data (attrition bias)	Low risk	Number of patients in both groups remained above number required by power analysis. Data from the efficacy- evaluable population is reported, not all who were randomized.
Selective reporting (reporting bias)	High risk	This study reports that the "final model retained site and body mass index as covariates" but this is never reported in the actual article.
Other bias	Unclear risk	Weight and height measured

Glasier 2011

Methods
Participants
Interventions
Outcomes

A secondary analysis of a systematic review meta-analysis
Included studies are Creinin 2006 & Glasier 2010
Performed a sub analysis based on BMI Groups: normal weight BMI < 25 kg/m² ; Overweight BMI 25-29.9 kg/m²; obese BMI >= 30 kg/m²
number of pregnancies



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Glasier 2010

Methods	RCT, meta-analysis
Participants	<p>Setting: 35 family planning clinics across the United Kingdom, Ireland, and USA.</p> <p>Randomized: 2221 eligible women enrolled and randomized, 1104 assigned to ulipristal acetate and 1117 assigned to levonorgestrel</p> <p>Age: 24.5 ±6.1 years for ulipristal acetate and 24.9±6.5 years for levonorgestrel</p> <p>Completed: 2133 completed the study: 48 lost to follow-up for ulipristal acetate and 20 lost to follow-up for levonorgestrel</p> <p>Gender: all participants were female. 1696 women's data were used for final analysis that reviewed women who had emergency contraception within 72 hours after unprotected sex and were 35 years of age or younger.</p> <p>Inclusion criteria: Women with regular menstrual cycles (24-35 days) seeking emergency contraception within 120 hours of unprotected sexual intercourse.</p> <p>Exclusion criteria: Women who were pregnant, breastfeeding, sterilized, fitted with an intrauterine device, taking hormonal contraception, or whose partners were sterilized were excluded.</p> <p>Power analysis: 1654 women would be needed to reach at least 85% power to show non-inferiority of ulipristal acetate versus levonorgestrel when taken within 72 hours of sexual intercourse. Taking into account additional women to be enrolled between 72 hours and 120 hours, and an anticipated rate of loss to follow-up of 10%, we planned to enroll 2044 women.</p>
Interventions	<p>Intervention: Enrolled women were randomly assigned to receive ulipristal acetate 30mg or levonorgestrel 1.5mg given orally. The randomization schedule was stratified by site and time from unprotected sexual intercourse to treatment (within 72 hours and 72-120 hours) with a block size of four.</p>
Outcomes	<p>Outcomes: EC failure at 0-24 hours, 25-48 hours, 49-72 hours, 73-96 hours and 97-120 hours</p>
Notes	

Risk of Bias Table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Block randomization was stratified by center and time from unprotected sexual intercourse to treatment.
Allocation concealment (selection bias)	Low risk	Allocation concealment was completed by identical opaque boxes labeled with a unique treatment number.
Blinding of participants and	Low risk	Blinding of participants was ensured but investigators were not; this does not appear to



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personnel (performance bias)		influence outcome.
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessment was not blinded by investigators but does not appear to impact outcome analysis
Incomplete outcome data (attrition bias)	Low risk	No missing data found for outcomes. Data from the efficacy- evaluable population is reported, not all who were randomized.
Selective reporting (reporting bias)	Low risk	Study protocol is available and all of study's pre-specified data were included. However, they add data from a previous study in which the ULI was formulated as a capsule, and in this study they use a tablet with ULI that has been micronized.
Other bias	High risk	The sponsor of the study was involved in study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.
		Weight and height were self-reported.

Kapp 2015

Methods	A secondary analysis of a systematic review meta-analysis
Participants	Included studies are Creinin 2006 & Glasier 2010
Interventions	Performed a sub analysis based on BMI Groups: normal weight BMI < 25 kg/m ² ; Overweight BMI 25-29.9 kg/m ² ; obese BMI >= 30 kg/m ² on LNG only
Outcomes	number of pregnancies
Notes	By combining the two studies, the power analysis from Creinin 2006 and Glasier 2010 was met for the LNG only comparison.



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	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Crenin 2006	+	+	+	?	+	-	+
Glasier 2010	+	+	+	+	+	+	-

Figure 1. Risk of Bias Summary



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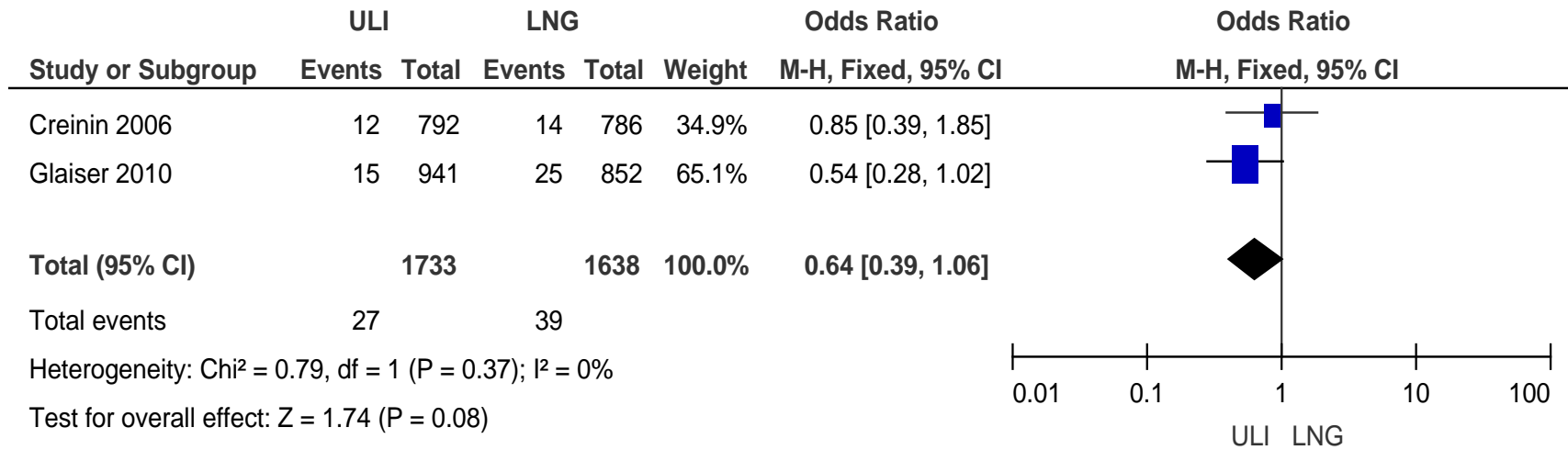


Figure 2. ULI vs. LNG (Modified ITT or Per Protocol analysis), Outcome: Treatment failure (lower is better) Overall



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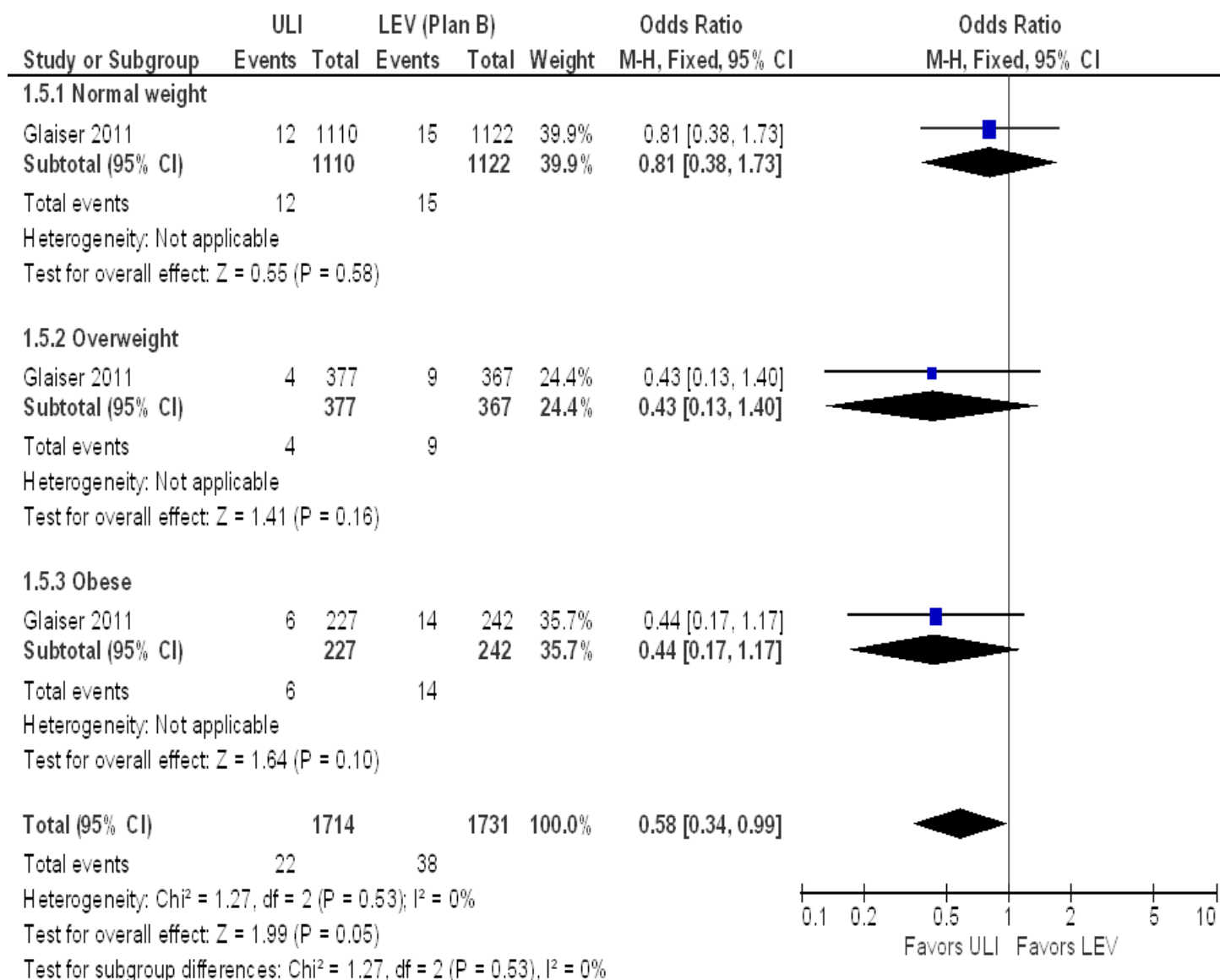


Figure 3. Ulipristal vs. Levonorgestrel, Outcome: Treatment failure (lower is better) by BMI



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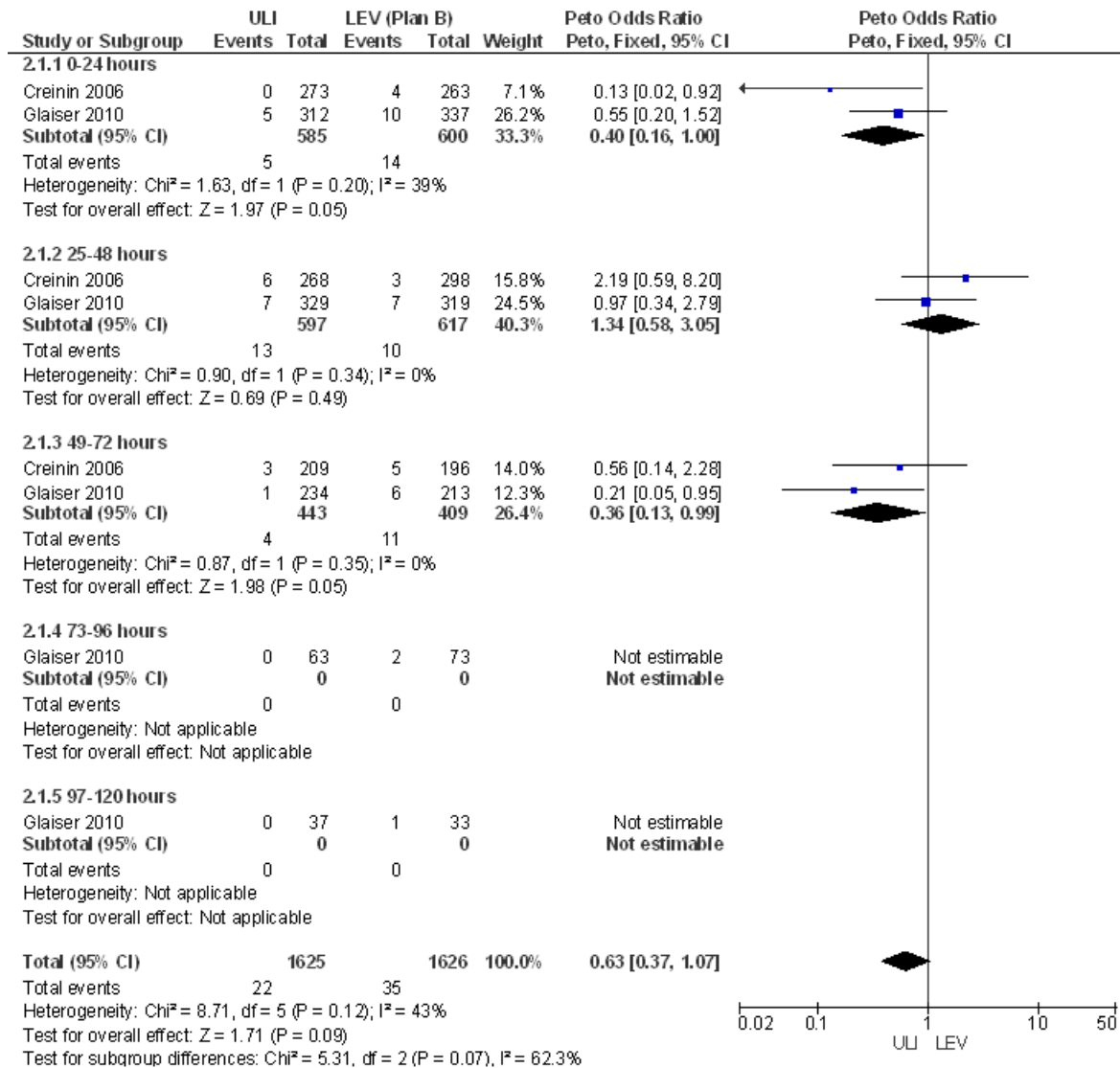


Figure 4. Ulipristal vs. levonogestrel, Outcome EC failure (pregnancy) by time to treatment



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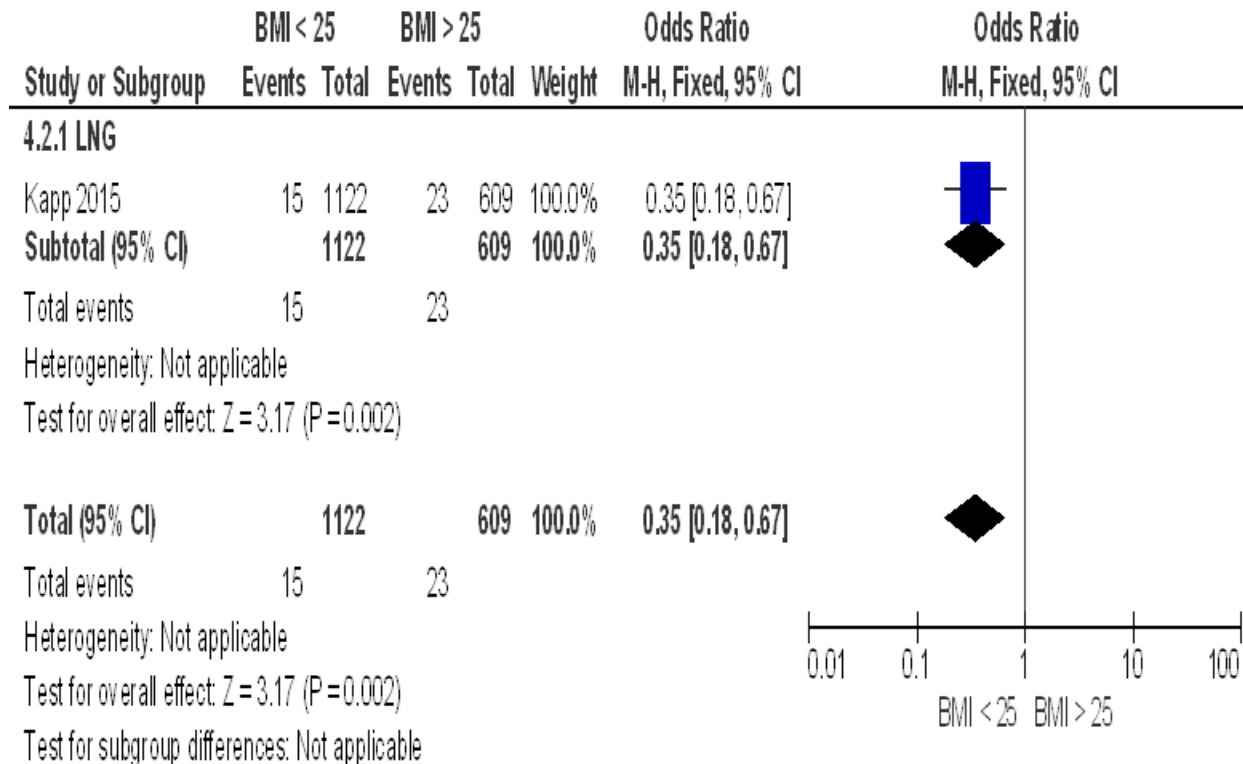


Figure 5. BMI < 25 kg/m² vs. BMI > 25 kg/m², Outcome: Treatment failure when treated with LNG alone (lower is better)



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