

Strategies for data analysis: I. Observational studies

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What strategy of analysis?

Objectives of the study



- Type of study
- Study design



Strategy of analysis

Objectives of the study

- Descriptive
- Comparative: estimation and test of hypothesis about the effect of a treatment or exposure on an outcome
- Model building

Types of studies

- Censuses and surveys
 - Cross-sectional study
 - Cohort studies
 - Case-control studies
 - Experimental studies
- Observational
-

Cross-sectional studies

Association between birthweight and maternal age

Maternal age	Birthweight		Total
	≤ 2500 g	> 2500 g	
≤ 20 years	10	40	50
> 20 years	15	135	150
Total	25	175	200

Cross-sectional studies

Association between birthweight and maternal age

Maternal age	Birthweight		Total
	≤ 2500 g	> 2500 g	
≤ 20 years	5%	20%	25%
> 20 years	7.5%	67.5%	75%
Total	12.5%	87.5%	100

Cohort studies

Association between birthweight and maternal age

Maternal age	Birthweight		Total
	≤ 2500 g	> 2500 g	
≤ 20 years	20	80	100
> 20 years	10	90	100
Total	30	170	200

Cohort studies

Association between birthweight and maternal age

Maternal age	Birthweight		Total
	≤ 2500 g	> 2500 g	
≤ 20 years	20%	80%	100%
> 20 years	10%	90%	100%

Cohort studies

Difference in rates of low birthweight between mothers >20 years and mothers ≤20 years:

$$\text{Diff} = 20\% - 10\% = 10\%$$

Relative risk of low birthweight of mothers ≤20 years compared with mothers >20 years:

$$\text{RR} = 20\% / 10\% = 2$$

Cohort studies

Odds of low birthweight of mothers ≤ 20 years :

$$20\% / 80\% = 0.25$$

Odds of low birthweight of mothers > 20 years :

$$10\% / 90\% = 0.11$$

Odds ratio of low birthweight of mothers ≤ 20 years compared with mothers > 20 years:

$$OR = (20/80) / (10/90) = 2.25$$

Case-control studies

Association between birthweight and maternal age

Maternal age	Birthweight		Total
	≤ 2500 g	> 2500 g	
≤ 20 years	40	23	63
> 20 years	60	77	137
Total	100	100	200

Case-control studies

Association between birthweight and maternal age

Maternal age	Birthweight	
	≤ 2500 g	> 2500 g
≤ 20 years	40%	23%
> 20 years	60%	77%
Total	100%	100%

Case-control studies

Difference in proportions of mothers ≤ 20 years between babies ≤ 2500 g and babies > 2500 g:

$$\text{Diff} = 40\% - 23\% = 17\%$$

If the exposure distribution among controls is the same as in the source population of cases, the RR can be estimated by the exposure OR:

$$\text{RR} = 40 \times 77 / 60 \times 23 = 2.23$$

(RR of low birthweight of mothers ≤ 20 years compared with mothers > 20 years)

Analysis of a comparative multicentre cross-sectional study

- Define analysis population according to protocol
- Describe prognostic variables by exposure group
- Provide crude effect of risk factor on outcome measure
- Provide effect of risk factor on outcome measure adjusting for possible confounders
- Look for effect modifiers and conduct stratified analysis

Define analysis population

- Count recruited subjects, decide on exclusions according to protocol and on numbers of eligible subjects by exposure group and by centre
- Look for missing data on the main outcome among eligible subjects and compute numbers of subjects to be included in the analysis by exposure group and by centre

Describe prognostic variables by exposure group

- Compute, by exposure group:
 - means and standard deviations (continuous variables)
 - medians and quartiles (discrete variables)
 - percentages (categorical variables)
- Compare prognostic variables between exposure groups to discover possible confounders

Comparison of prognostic variables between exposure groups

Comparison is made by assessing the prognostic relevance of the difference observed, **not using tests of hypothesis:**

‘Confounding of the treatment effect by extraneous factors is a distortion within a body of data; statistical tests of significance are directed at the question of inference beyond the data in hand...(and) is clearly immaterial’

Rothman, 1977

Comparison of prognostic variables between exposure groups

‘The extent to which an extraneous factor can distort the assessment of the treatment effects depends on two relationships:

- the extent of the imbalance of the extraneous factor among the groups
- the degree to which the extraneous factor is associated with the outcome under study’

Rothman, 1977

Estimate crude effect of risk factor

- Estimate the magnitude of the effect adjusting for confounding
- Give confidence intervals for the effect, not just p-values:
‘The p-value...incorporates information on the magnitude of the effect and the precision with which the effect is measured, and thus inevitably fails to provide distinct information about each of these...Confidence intervals convey information about both magnitude of effect and precision...’

Rothman, 1986

Adjust the effect of the risk factor for possible confounders

- Determine possible confounders:
 - Variables with imbalance between groups
 - Variables related to outcome: perform analyses to examine association between different variables and the outcome
- Adjust for confounders:
 - Include confounders in a multivariate model
 - Account for collinearity between variables in the model

Look for effect modifiers: stratified analysis

- Look for effect modifiers in stratified analyses (for example, centre)
- Test interactions
- If there are important effect modifiers, present a stratified analysis

Steroid hormone contraception and bone mineral density: a cross-sectional study in a diverse international population

Objective: to assess peak bone mass according to steroid hormonal contraceptive use.

Methods: cross-sectional study done at 7 centres in three geographic regions of the developing world. Women of 30-34 years of age attending family planning clinics who had at least 24 months of lifetime use of combined oral contraceptives (COC), depot-medroxyprogesterone (DMPA) or Norplant were recruited along with a comparison group of never users. Bone mineral density was measured at two sites.

Sample size calculation

Objective: to detect a difference of 1/2 SD between two BMD means in a two-sided 5% level test with a power of 80%.

The number of women per group is

$$n = \frac{2(Z_{\alpha/2} + Z_{\beta})^2 \sigma^2}{\Delta^2} = \frac{2(Z_{\alpha/2} + Z_{\beta})^2}{\partial^2}$$

$$n = \frac{2(1.96 + 0.842)^2}{0.5^2} = 63$$

n was taken as 125 per group to allow for a sub-group comparison

Strategies for data analysis: II. Randomized controlled trials

Gilda Piaggio

*UNDP/UNFPA/WHO/World Bank Special Programme of
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Human Reproduction
World Health Organization*

Geneva, 19 September 2001

Study design

For experimental studies:

- Completely randomized
- Paired-matched
- Stratified
- Cluster randomized
- Cross-over

Analysis of a multicentre randomized controlled trial

- Provide a trial profile
- Describe prognostic variables by treatment group
- Provide crude effect of treatment on outcome measure
- Provide effect of treatment on outcome measure adjusting for possible confounders
- Look for effect modifiers and conduct stratified analyses

Trial profile

Construct a flow chart providing numbers of:

- registered or eligible subjects
- randomized subjects
- subjects assigned to each group

and for each group,

- subjects withdrawn (lost to follow-up and other reasons)
- subjects who completed the trial (with outcome known)
- subjects who did not receive or comply with the treatment as allocated

Protocol deviations in the analysis

- Ineligible patients
 - inclusion of all randomized subjects guards against any bias incurred by subjective choice of ineligible subjects
 - inclusion better if the trial's findings are to be extrapolated to future clinical practice in which eligibility for a given treatment is less-strictly defined
 - can be excluded when eligibility criteria are clear and objective and when the trial is double-blind

Protocol deviations in the analysis

- Non-compliance and withdrawals: analysis should be done by ‘**intention to treat**’ principle (pragmatic approach)

‘...all eligible patients, regardless of compliance with protocol should be included in the analysis of results whenever possible’

‘The alternative ‘explanatory approach’ or ‘analysis of compliers only’ can distort treatment comparisons’

Pocock, 1983

Protocol deviations in the analysis

Intention to treat is not possible or can be relaxed:

- when outcome is not known (for example, in withdrawals)
- when a subject withdraws before treatment starts (caution: check if numbers and reasons are similar between groups)
- in Phase I and Phase II clinical trials, which explore properties of treatment in idealized conditions

Comparison of baseline characteristics between treatment groups

Comparison is made by assessing the prognostic relevance of the difference observed, **not using tests of hypothesis:**

- Compute sample statistics (means and standard deviations or medians and quartiles or percentages) by treatment group
- Compare baseline characteristics between treatment groups to discover possible confounders: randomization will produce very similar baseline statistics if the sample size is large

Estimate crude effect of treatment

- Estimate the **magnitude** of the effect and compute a confidence interval
- A p-value can also be provided

Adjust the effect of the treatment for possible confounders

- Use same procedure described for observational studies to determine possible confounders
- Confounding is not as important as in observational studies because randomization will produce balance between treatment groups

Presentation

- Describe protocol deviations from the study as planned, together with the reasons (for ineligibility, non-compliance, withdrawal)
- Percentages: state results in absolute numbers (10/20, not only 50%)
- Present statistics in sufficient detail to permit alternative analyses and replication

Look for effect modifiers: stratified analysis

- Stratify by centre
- Test homogeneity of effect across centres (and/or test interaction of treatment by centre)
- If there is homogeneity between centres, pool the effect over centres (adjust effect for centres)
- Consider other effect modifiers

Interpretation

- State findings clearly
- Discuss internal validity: sources of bias and imprecision
- Discuss external validity

Levonorgestrel versus the Yuzpe regimen for emergency contraception: a randomized controlled trial (WHO Project 92908)

*Research Group on Research of Post-Ovulatory Methods
UNDP/UNFPA/WHO/World Bank Special Programme of
Research, Development and Research Training in
Human Reproduction
World Health Organization*

Washington, 13 April 1998

Objectives

- 1) To confirm that two doses of 0.75mg of levonorgestrel given 12 hours apart for emergency contraception have**
 - the same effectiveness but**
 - fewer side effects than the Yuzpe regimen**

- 2) To assess whether the same effectiveness can be achieved if the permissible delay between intercourse and the start of the treatment is extended (from 48 hours) to 72 hours.**

Design

- **Double-blind,**
- **randomized controlled trial**
- **conducted at 21 centres (14 countries) .**

- **Sample size calculation for an equivalence trial**

Characteristics of subjects

Treatment group	Yuzpe (n=979)		LNG (n=976)	
Variable	Mean	SD	Mean	SD
Age (years)	27.2	6.8	27.3	7.0
Weight (kg)	58.6	9.6	58.4	10.4
Height (cm)	162.8	6.5	162.9	6.4
BMI (kg/m ²)	22.1	3.3	22.0	3.6
Cycle length (days)	28.8	2.5	28.9	2.4
Interval from estimated ovulation to intercourse (days)	-1.0	5.2	-0.9	5.0

Pregnancy rates

Group	Number of women	Observed pregnancies	Pregnancy rate (%)	95% CI
Yuzpe	979	31	3.2	(2.2, 4.5)
LNG	976	11	1.1	(0.6, 2.0)

Relative risk (RR) of pregnancy for LNG compared with Yuzpe:

RR	95% CI
0.36	(0.18, 0.70)

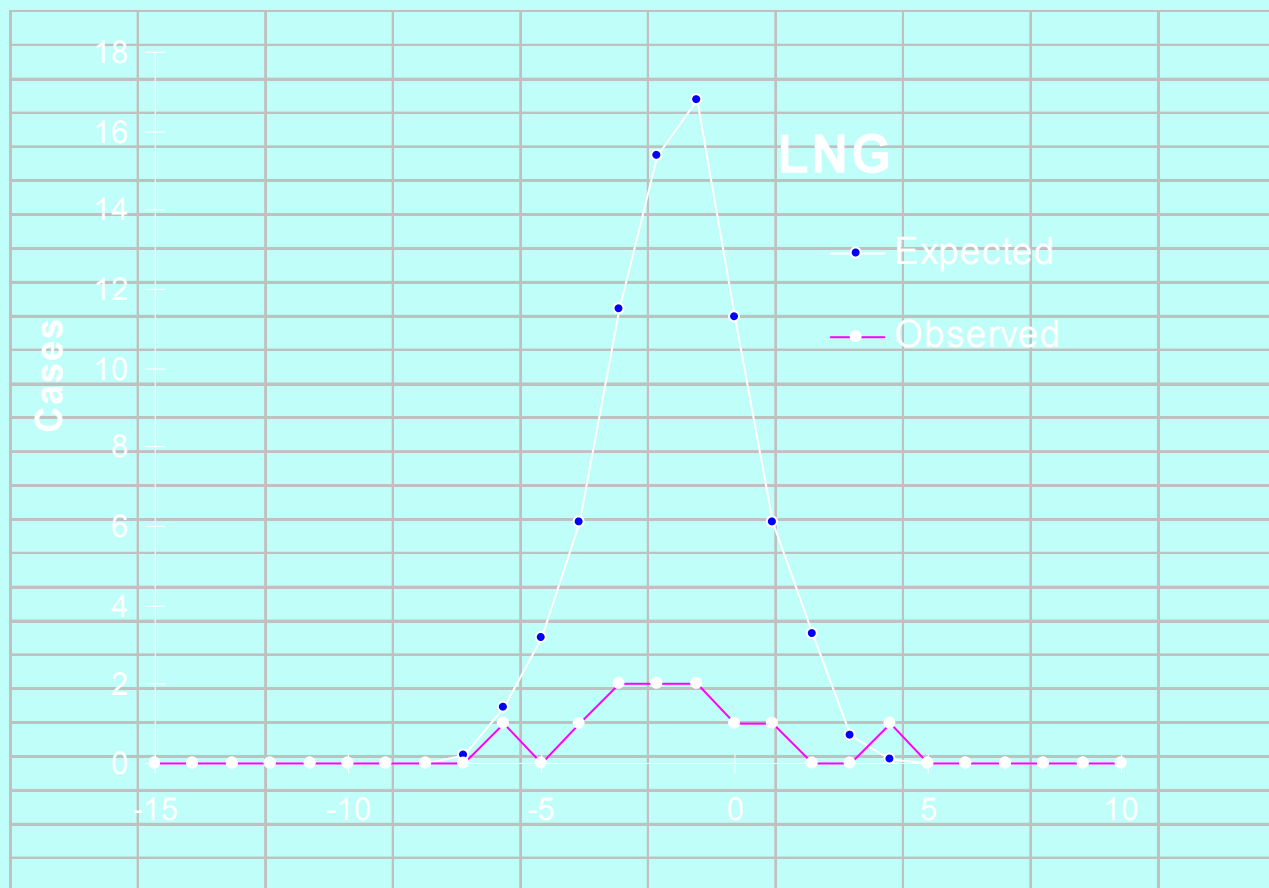
Pregnancy rates

Group	Number of women	Observed pregnancies	Pregnancy rate (%)	95% CI
Efficacy Intent-to-treat Population:				
Yuzpe	979	31	3.2	(2.2, 4.5)
LNG	976	11	1.1	(0.6, 2.0)
Eligible Population:				
Yuzpe	922	23	2.5	(1.6, 3.8)
LNG	933	8	0.9	(0.4, 1.7)
Perfect use population:				
Yuzpe	583	11	1.9	(1.0, 3.4)
LNG	574	5	0.9	(0.3, 2.0)

Relative risk (RR) of pregnancy of LNG with respect to Yuzpe: main and secondary analyses

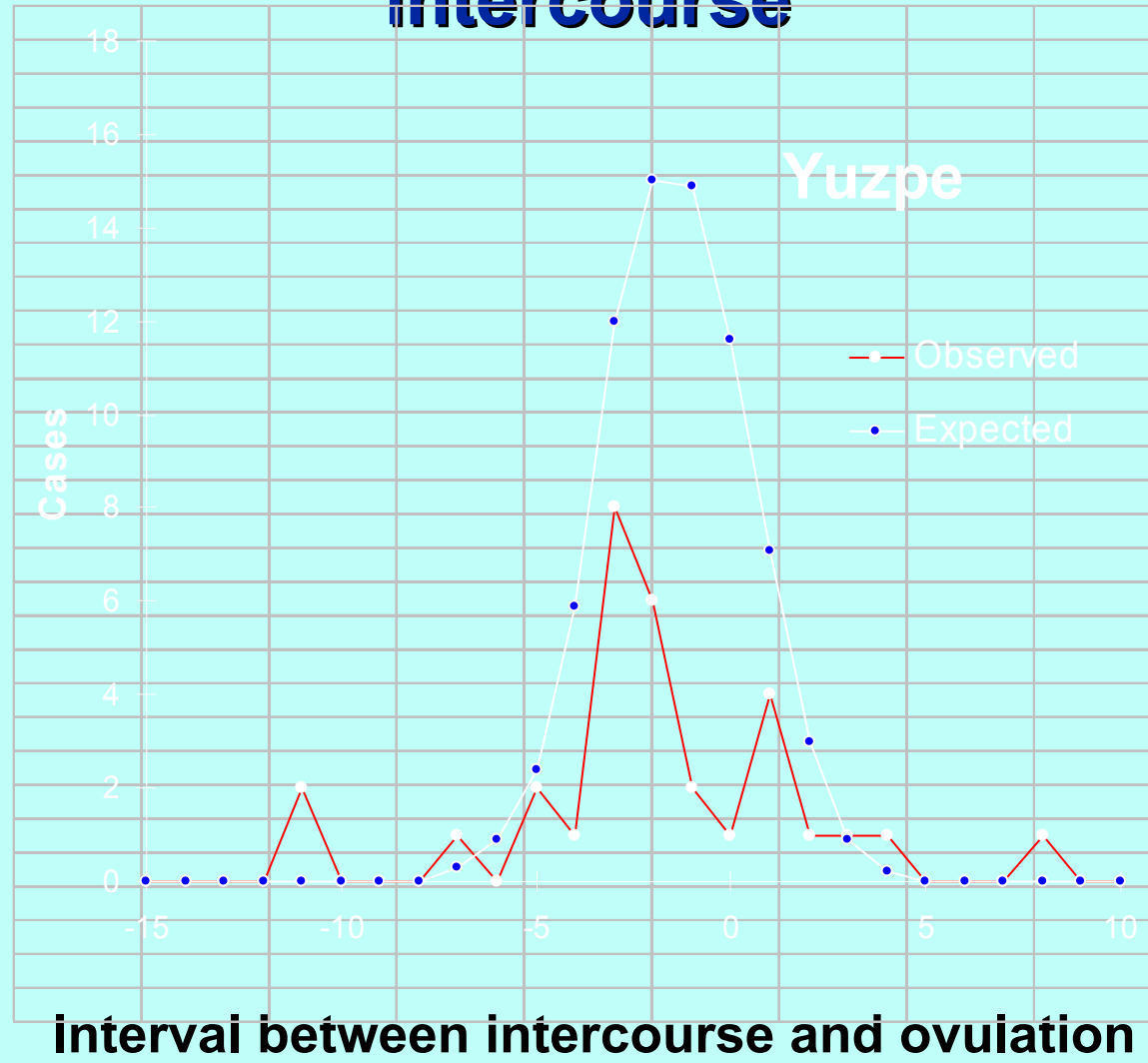
Population	No. of women	No. of pregnancies	RR	95% CI
Efficacy ITT	1955	42	0.36	(0.18, 0.70)
Eligible	1855	31	0.34	(0.15, 0.76)
Perfect use	1157	16	0.46	(0.16, 1.32)

Observed vs expected pregnancies by day of intercourse



Interval between intercourse and ovulation (days)

Observed vs expected pregnancies by day of intercourse



Efficacy: prevented fraction

Group Efficacy**	No. of women	No. of pregnancies			
		Observed	Expected*	(%)	95% CI
Yuzpe	979	31	74.2	58	(41, 72)
LNG	976	11	76.3	86	(74, 93)

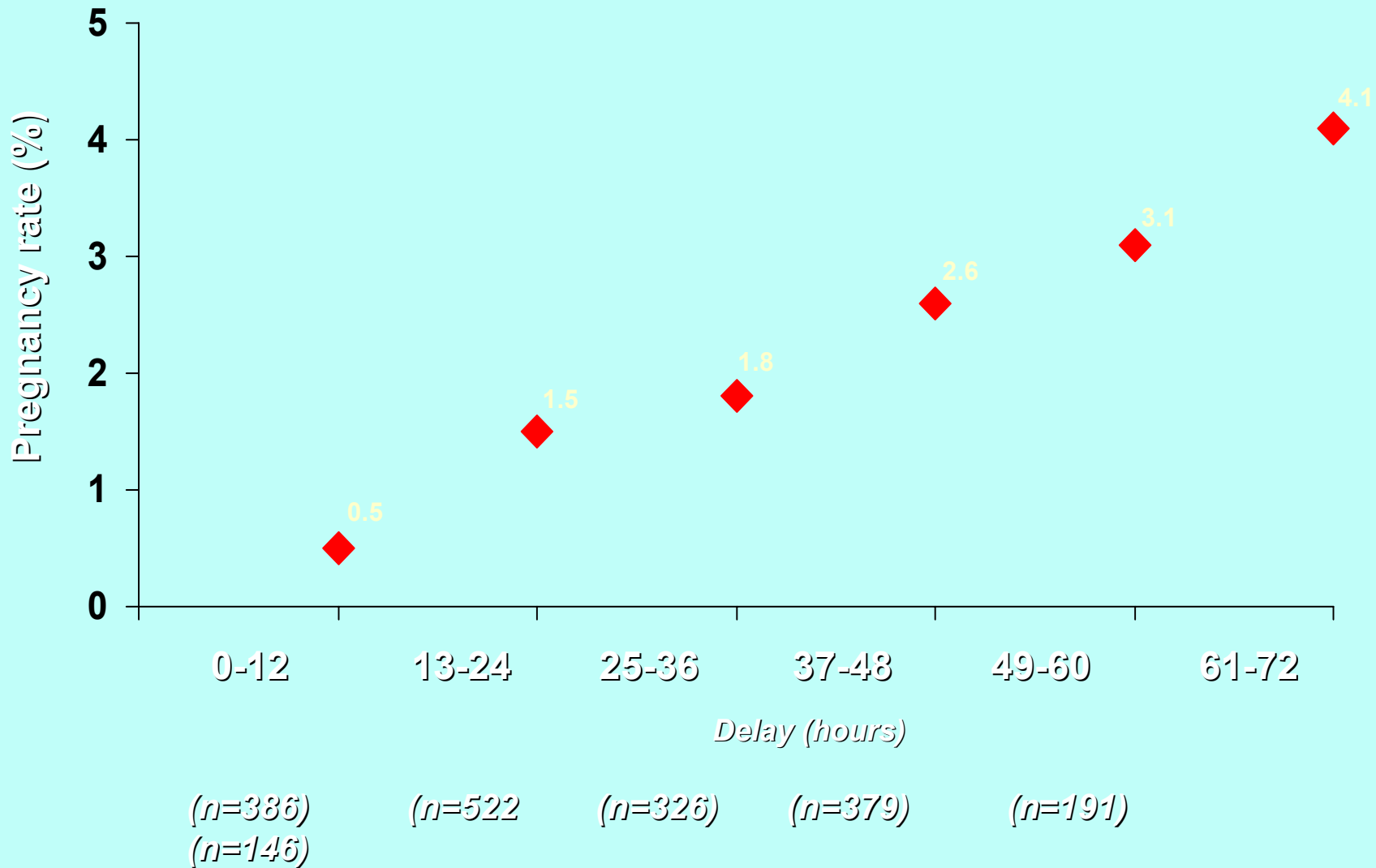
* Using Dixon's estimates of conception probabilities

** Prevented fraction

Ratio of standardized pregnancy rates of LNG with respect to Yuzpe:

Ratio	95% CI
0.34	(0.16, 0.70)

Effect of delay on pregnancy rates



Incidence of side effects

Side effect	Yuzpe		LNG		p-value
	No. of Cases	Rate (%)	No. of Cases	Rate (%)	
Nausea	494	50.5	226	23.1	<0.01
Vomiting	184	18.8	55	5.6	<0.01
Headache	198	20.2	164	16.8	0.06
Dizziness	163	16.7	109	11.2	<0.01
Fatigue	279	28.5	165	16.9	<0.01

Conclusions

- **The LNG regimen is more effective than the Yuzpe regimen.**
- **It is better tolerated.**
- **With both regimens, earlier treatment is more effective.**

Sample size calculation

Objective: to detect a minimum difference in the proportion of low birthweight babies between 10% and 12% between two groups of women (≤ 20 years, > 20 years) in a two-sided 5% level test with a power of 80%.

The number of women per group is

$$n = \frac{(Z_{\alpha/2} + Z_{\beta})^2 [P_1(1 - P_1) + P_2(1 - P_2)]}{(P_1 - P_2)^2}$$

$$n = \frac{(1.96 + 0.842)^2 [0.10(1 - 0.10) + 0.12(1 - 0.12)]}{(0.10 - 0.12)^2} = 3841$$