Long term follow-up of one-rod etonogestrel (ENG) and two-rod levonorgestrel (LNG) contraceptive implants: comparing effectiveness, continuation rates and adverse effects

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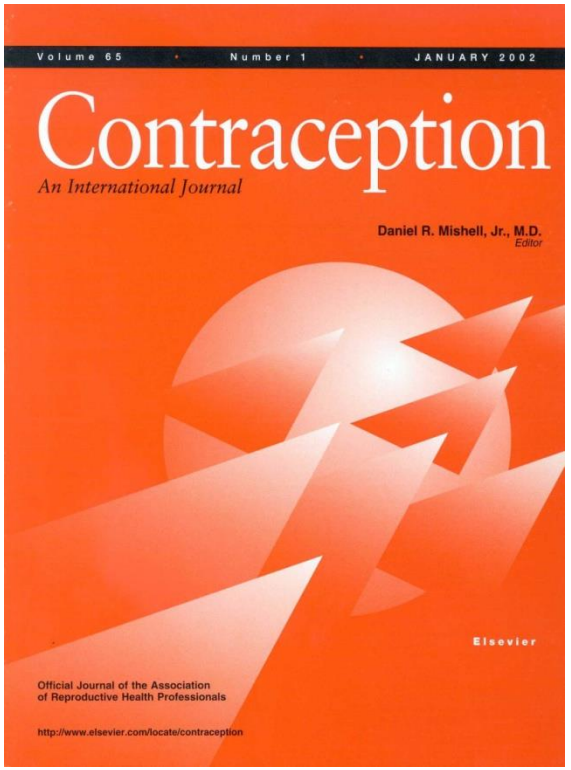
Presentation outline

- Background
- Objectives of the study
- Methodology
- Description of population enrolled
- Key findings on effectiveness, adverse events and method continuation

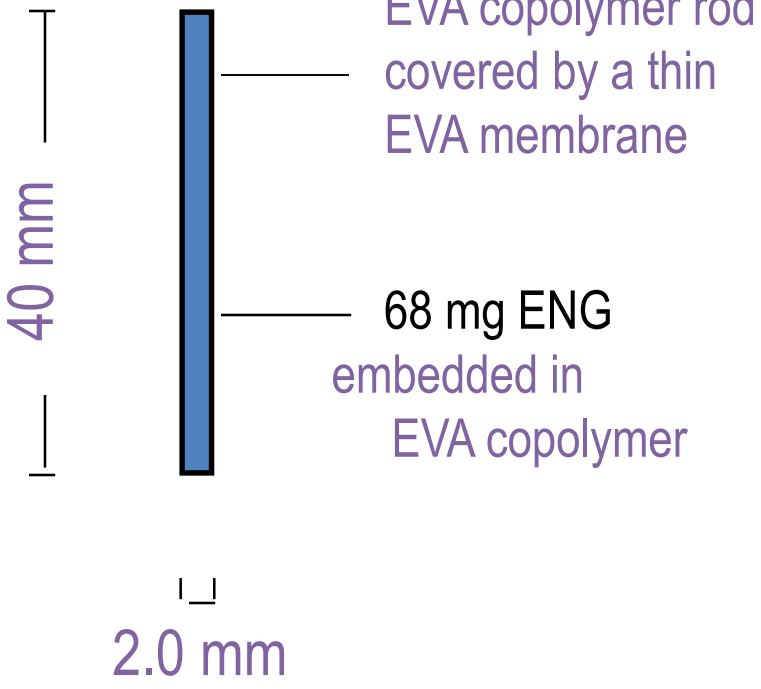
WHO Consultation on Implantable Contraceptives for Women 2001

- Review on safety and effectiveness of available implantable contraceptives for women. Published in an issue of *Contraception 65 (1) 2002*.
- Levonorgestrel and etonogestrel implants are highly effective and safe (annual pregnancy rates in the order of 0.0-0.5 per 100 women)
- No comparative trial of Jadelle and Implanon had been done
- Lack of reliable data on common non-serious side effects typically attributed to progestins
- Consideration to extend the trial up to 5 years if justified by initial data.

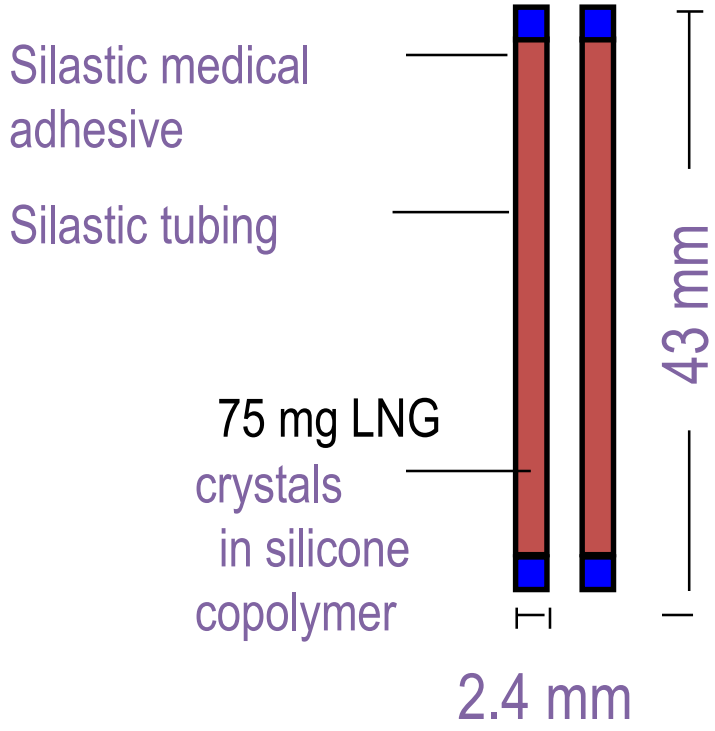


Second generation contraceptive implants

One-rod Etonogestrel
Approved duration of use: 3 yrs

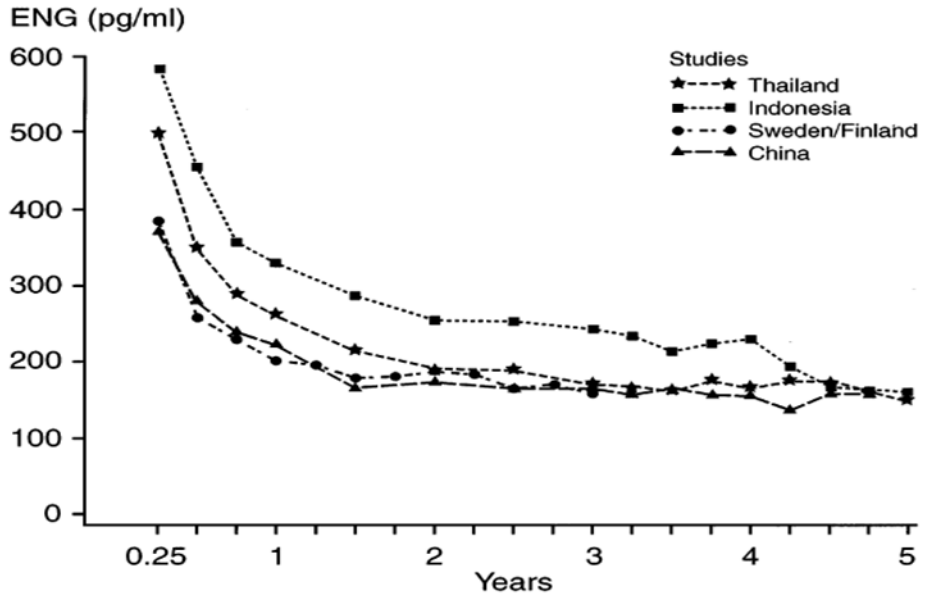


Two-rod Levonorgestrel
Approved duration of use: 5 yrs.



Rationale for study extension at end of year 3

- Few pregnancies reported for the etonogestrel implant during 3 years of use
- Pharmacokinetic data indicated ENG implant likely to be effective for contraception beyond 3 years of use



Huber J. Contraception 1998

Main objectives

Primary objectives

- Compare the contraceptive effectiveness of both models of implants.
- Compare annual, 3-year, cumulative rates of methods continuation of two-rod LNG and one-rod ENG.
- Compare the incidence of AEs between women using implants and those using the copper IUD.

Subsidiary objectives

- Compare between the three contraceptives, reasons for method discontinuation.

Study Design and Ethics approval

- Randomized, open, parallel-group controlled clinical trial (RCT)
- Non-randomized control group of age-matched women choosing IUD and accepted to be followed simultaneously.
- Study approved by the Scientific and Ethical Review Group at HRP/WHO and the WHO Secretariat Committee on Research Involving Human Subjects.
- Local or national Ethics Committee at each center.

Participating centers and number of enrolled participants: Enrollment from May 2003-January 2008

	ENG implant	LNG implant	TCu380A	Total
Brazil	130	130	130	390
Chile	160	160	161	481
Dominican Rep	209	208	209	626
Hungary	95	98	77	270
Thailand	169	169	162	500
Turkey	100	100	95	295
Zimbabwe	140	140	140	420
All centers	1003	1005	974	2982
Per protocol population	**995**	**997**	**971**	**2965**

Duration of implant insertion:

time from when the scalpel or the applicator needle first touch the skin until placement of sterile dressing

	2-rod LNG n=995	1-rod ENG n=992
Mean duration (secs)	88 ± 60.8*	51 ± 50.2
Median duration (secs)	70	40

* Mean difference 37 sec (95% CI; 33-41) p<0.0001

Duration of removal procedure:

time from when the scalpel first touches the skin until sterile dressing or a compress is placed on the site of the removal

	2-rod LNG n=292	1-rod ENG n=334
Mean duration (secs)	156.5 ± 147.5*	98.0 ± 99.4
Median duration (secs)	120	70
Range	4-1200	4-903

* Mean difference 58.5 secs

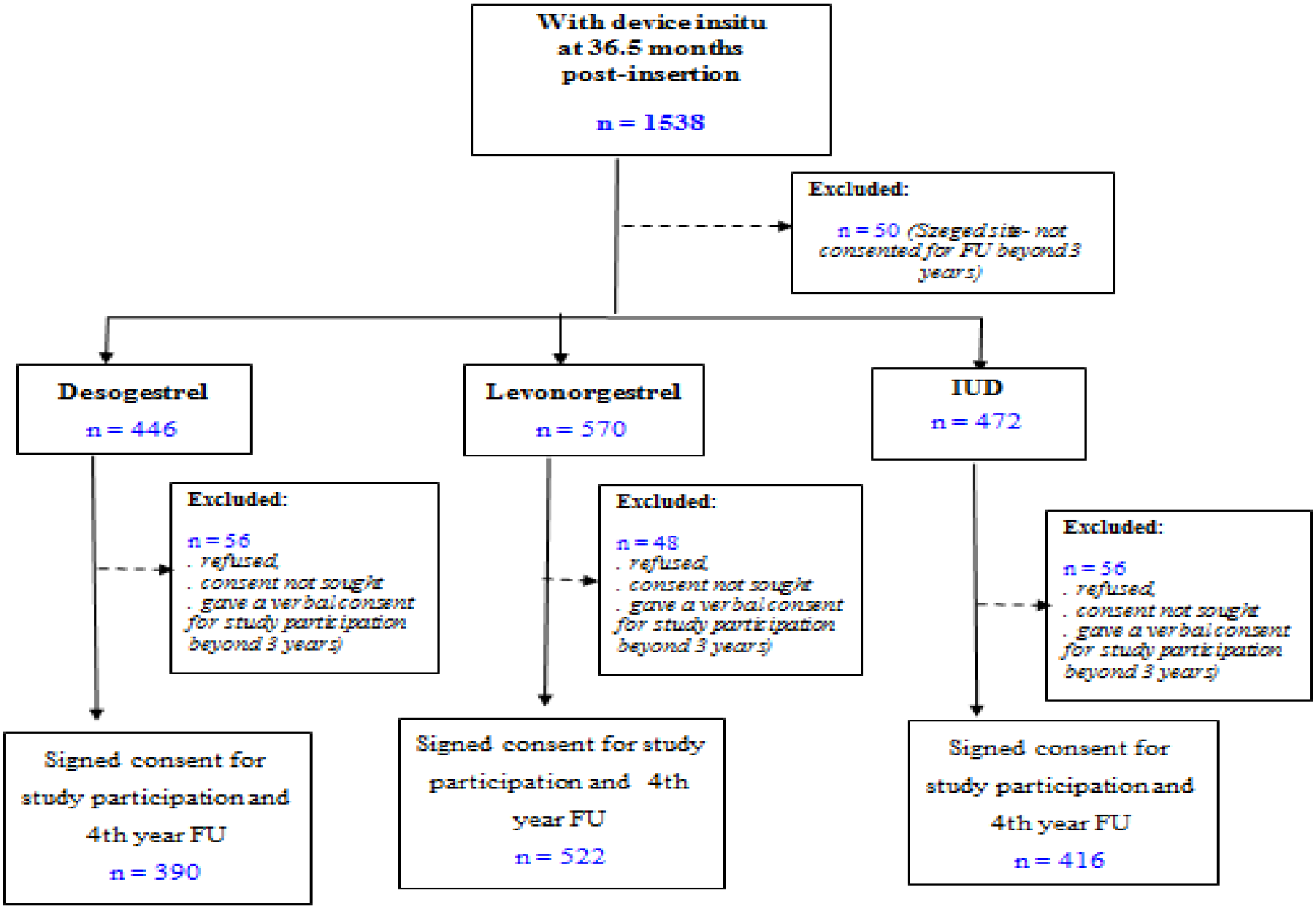
Contraceptive effectiveness - Three years Follow up

		IUD		2-rod LNG		1-rod ENG	
Endpoint	**Time from device insertion (months)**	**At risk /events (cum)**	**Rate (95%CI)**	**At risk /events (cum)**	**Rate (95%CI)**	**At risk /events (cum)**	**Rate (95%CI)**
Pregnancy							
At risk at the beginning of the interval	Year 1: 0-12 months	971/9	1.12 (0.59, 2.15)	997/0	0	995/1	0.11 (0.02, 0.78)
At risk at the beginning of the interval	Year 2: 13-24 months	698/10	1.29 (0.69, 2.38)	843/0	0	857/1	0.11 (0.02, 0.78)
At risk at the beginning of the interval	Year 3: 25-36 months	571/14	2.84 (1.33, 6.00)	721/3	0.44 (0.14, 1.35)	717/3	0.43 (0.14, 1.35)

Study beyond three years – primary objectives

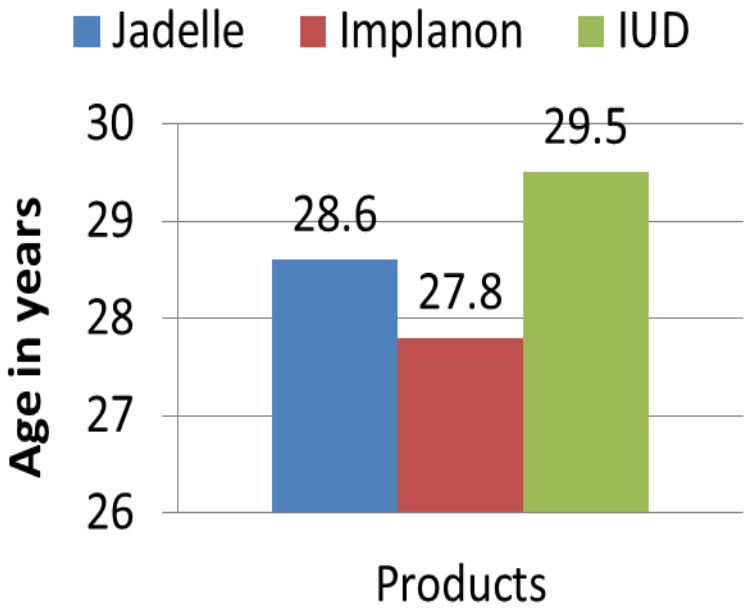
- Study contraceptive effectiveness of Implanon use beyond three years
- Compare clinical performance, safety and continuation of 1-rod ENG to 2-rod LNG, and with IUD (TCu380A)
- Extended trial was conducted in all participating centers, except Hungary
- Cohort study – extended 2 year follow-up study of participants (no longer a RCT).

Flow chart – beyond three years of follow up



Participants characteristics

- **Age*** – slightly higher in IUD group than implants
  - (more under 35 years among implants)
- **Education*** – IUD more so up to Primary level and implants more so among secondary level education
- IUD more common among housewives, while implants more among professionals/workers
- Implants slightly more used by nulligravida
- **BMI*** – IUD users had higher BMI compared to implants users, while no differences among implants users



Jadelle: (n=522)
Implanon: (n=390)
IUD: (n=416)

By end of 24 months of follow up …

Method continuation

- 12 months – IUD group 91%, 2-rod LNG 91%, 1-rod ENG 81%
- 18 months –IUD group 84%, 2-rod LNG 86%, 1-rod ENG 73%
- 23 months –IUD group 74%, 2-rod LNG 64%, 1-rod ENG 54%
- 24 months –IUD group 52%, 2-rod LNG 13%, 1-rod ENG 12%

By end of 24 months of follow up … discontinuation reasons

Discontinuation reasons	IUD n:416	Rates (95% CI)	2-rod LNG n: 522	Rates (95% CI)	1-rod ENG n: 390	Rates (95% CI)
Expulsion	416/7	1.9 (0.9-4)	522/0	0	390/0	0
Bleeding	416/18	4.7(3.0-7.4)	522/11	2.3 (1.3-4.0)	390/11	3.4 (1.9-6.1)
Wish to be pregnant	416/33	8.7 (6.2-12.0)	522/28	5.7 (4.0-8.2)	390/30	8.4 (5.9-11.9)
All medical reasons combined	416/28	7.3 (5.1-10.4)	522/13	2.7 (1.6-4.6)	390/11	3.4 (1.9-6.1)
All non-medical reasons	416/48	12.2 (9.1-15.9)	522/72	14.2 (11.4 – 17.6)	390/98	25.8 (21.7-30.5)

All medical reasons: expulsions, perforations, bleeding and other medical reasons
All non medical reasons: wish to be pregnant, out of reach, no longer willing to continue and other personal

By end of 24 months of follow up … common AE (*contd*)

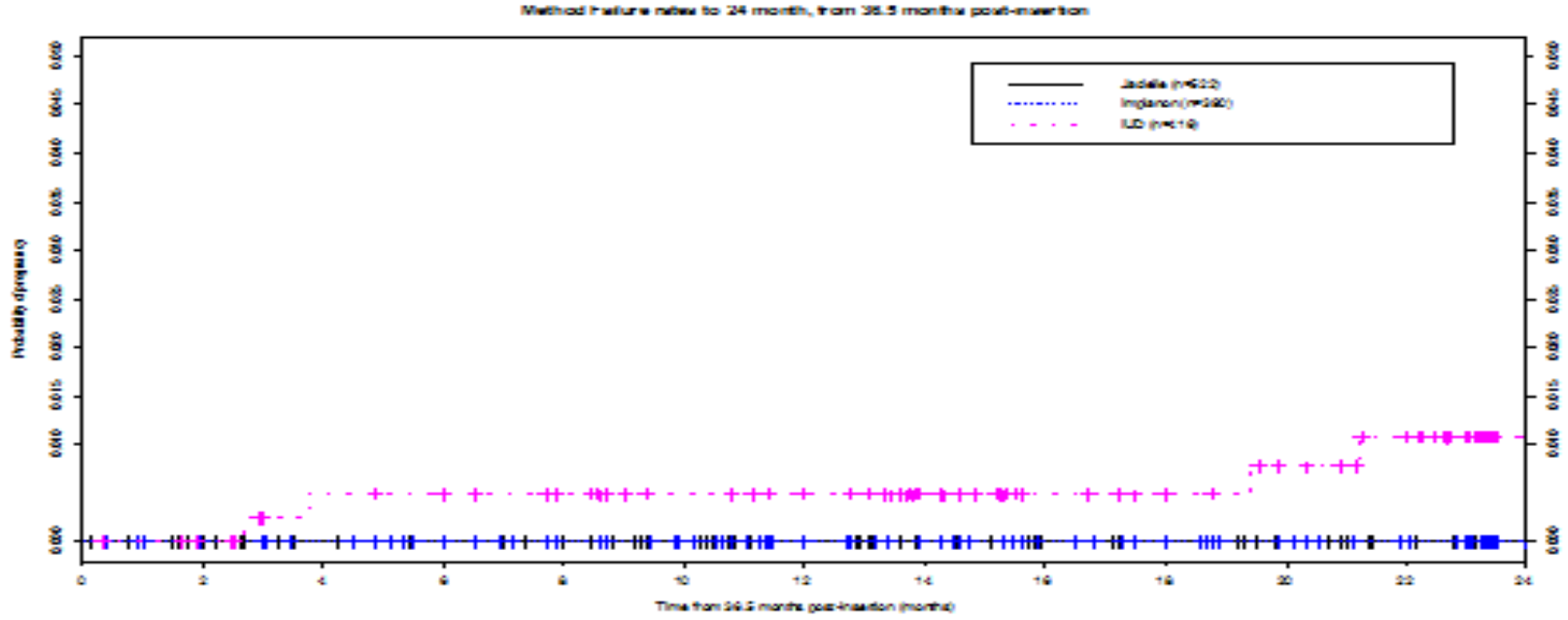
- **Headache**
  - Among implants - no significant difference
  - Comparing IUD and implants - no difference
- **Dizziness**
  - Among implants - no significant difference
  - Comparing IUD and implants - no difference
- **Acne**
  - Among implants - no significant difference
  - Comparing IUD and implants – more among implant users
- **Lower abdominal pain**
  - Among implants - no significant difference
  - Comparing IUD and implants – more among IUD users

By end of 24 months of follow up … common AE

- **Amenorrhea**
  - Among implants - no significant difference (slightly more in 1-rod ENG)
  - Comparing IUD and implants – more among implant users
- **Heavy bleeding**
  - Among implants - More among 1-rod ENG users
  - Comparing IUD and implants – more among IUD users
- **Prolonged bleeding**
  - Among implants - no significant difference
  - Comparing IUD and implants – more among implant users
- **PID**
  - Among implants - no significant difference
  - Comparing IUD and implants - no significant difference (slightly more in IUD)

Contraceptive effectiveness

Endpoint	Time from 36.5 months post-device	IUD: At risk /events (cum)	IUD: Rate (95%CI)	2-rod LNG: At risk /events (cum)	2-rod LNG: Rate (95%CI)	1-rod ENG: At risk /events (cum)	1-rod ENG: Rate (95%CI)	Both implants: At risk /events (Cum)	Both implants: Survival Rate (95% CI)
Pregnancy									
	15 days	416/0	0.0	522/0	0.0	390/0	0.0	912/0	0.0
	12 mo	384/2	0.5 (0.1, 1.9)	482/0	0.0	345/0	0.0	827/0	0.0
	24 mo	256/4	1.0 (0.4, 2.9)	330/0	0.0	204/0	0.0	534/0	0.0



p-value (IUD vs Implant (Jadelle, Implanon): End of. 12mo p=0.038; 24 mo p=0.003:

Conclusions

- Evidence that, at the end of five years of follow up, both implant system are very comparable, providing effective and safe contraception
- Provide very important information regarding mild side effects associated with implant use as compared to IUD
- Benefit family planning programs:
  - Fewer implants needed to be purchased per user
  - Reduced number of insertions/removals
- Findings of the study can inform policy makers and clinicians about choice of implant, but also about TCu380A IUD in relation to implants