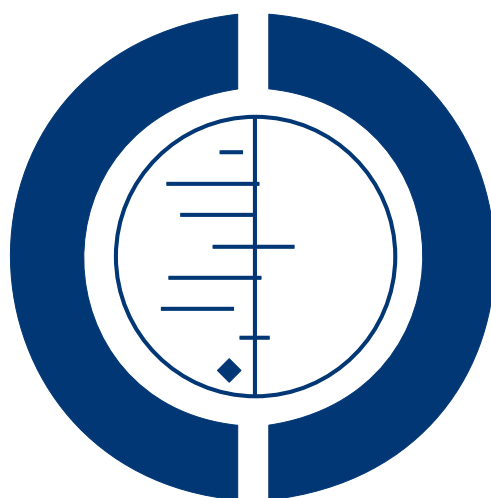


Frameless versus classical intrauterine device for contraception (Review)

O'Brien P, Marfleet CC



**THE COCHRANE
COLLABORATION®**

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2008, Issue 3

<http://www.thecochranelibrary.com>



TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	2
OBJECTIVES	2
METHODS	3
RESULTS	5
DISCUSSION	10
AUTHORS' CONCLUSIONS	13
ACKNOWLEDGEMENTS	14
REFERENCES	14
CHARACTERISTICS OF STUDIES	16
DATA AND ANALYSES	24
WHAT'S NEW	24
HISTORY	24
CONTRIBUTIONS OF AUTHORS	24
DECLARATIONS OF INTEREST	24
SOURCES OF SUPPORT	24
INDEX TERMS	25

[Intervention Review]

Frameless versus classical intrauterine device for contraception

Paul O'Brien¹, Caroline C Marfleet²

¹Raymede Clinic, Westside Contraceptive Services, Westminster Primary Care Trust, London, UK. ²Colchester, UK

Contact address: Paul O'Brien, Raymede Clinic, Westside Contraceptive Services, Westminster Primary Care Trust, Exmoor St, London, W10 6DZ, UK. paulobrien@nhs.net.

Editorial group: Cochrane Fertility Regulation Group.

Publication status and date: Edited (no change to conclusions), published in Issue 3, 2008.

Review content assessed as up-to-date: 12 November 2004.

Citation: O'Brien P, Marfleet CC. Frameless versus classical intrauterine device for contraception. *Cochrane Database of Systematic Reviews* 2005, Issue 1. Art. No.: CD003282. DOI: 10.1002/14651858.CD003282.pub2.

Copyright © 2008 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

The frameless intrauterine device (IUD) dispenses with the frame in the classical IUD and holds the device in the uterus by anchoring one end of a nylon thread in the fundal myometrium, to which copper sleeves are attached.

Objectives

This review examines the hypothesis that the frameless IUD Gynefix reduces risk of expulsion and pregnancy, and the problems of bleeding and pain necessitating early removal.

Search strategy

We searched the Cochrane Controlled Trial Register (Cochrane Library Issue 2, 2004), MEDLINE, and Popline from 1980 to March 2004, and reference list of articles.

Selection criteria

We selected for the review randomised trials that compared the frameless device to a classical framed device for contraception.

Data collection and analysis

Both authors extracted data independently. We contacted study author for additional data. We calculated rate ratios and rate differences for cumulative rates for each outcome at yearly intervals. We used the inverse variance-based method to combine trials, and tested the results for heterogeneity.

Main results

Four trials were included in the review involving 5,939 women randomised to either a frameless device or TCu380, with data up to eight years for the largest, and with a total experience of 23,180 years. Apart from one small trial, nulliparous women were excluded from the trials. The two earlier trials used a prototype introducer and there was a higher expulsion rate at one year (relative risk 2.48, 95% confidence intervals 1.89 to 3.26). However, between two and six years in the large WHO trial the risk of pregnancy was lower with the frameless device (relative risk 0.53, 95% confidence intervals 0.32 to 0.91). In a recent trial using GyneFix with a new introducer early expulsions and pregnancies were not statistically different from the control device. Removals rates for excessive bleeding and/or pain were no different between the devices (relative risks 0.92, 95% confidence intervals 0.74 to 1.14, at one year and 1.13, 0.93 to 1.37, at six years). There was a tendency towards fewer removals for pain in early years but no difference at six years (relative risk 1.13, 95% confidence intervals 0.93 to 1.37).

Authors' conclusions

There is insufficient data to show that problems of early expulsions have been overcome with the modified introducer used in GyneFix. Apart from that, the frameless device performs similarly to TCu380, and appears to have a lower pregnancy rate in later years, although the absolute difference is small.

PLAIN LANGUAGE SUMMARY

The frameless IUD performs similarly to traditional IUDs but does not reduce bleeding and pain associated with standard IUDs.

Devices placed in the uterus are highly effective at preventing pregnancy. Traditional intrauterine devices (IUD) with plastic frames have side effects such as excessive bleeding and pain that were thought to be due to the frame. This review found that symptoms of bleeding and pain, and contraceptive efficacy were not improved with the frameless device. Trials are needed to see if the frameless IUDs could benefit women who have not had children.

BACKGROUND

The intrauterine device (IUD) is, after female sterilisation, the most widely used method of contraception, with an estimated 127 million users worldwide in 1994 (Harrison 1996). Almost 90% of users are in developing countries. Theoretically the IUD is an ideal contraceptive. In contrast to oral contraception it requires no continuing motivation on the part of the user and its mechanism of action is local rather than systemic.

The use of devices deployed totally within the uterine cavity was developed in Germany in the 1920s. Intrauterine devices were used more widely in the 1930s but fell into disrepute because of reported complications, especially severe infections (Hawkins 1979). Against the background of a perceived need for world population control widespread interest in intra-uterine devices revived in the late 1950s (Tatum 1989). The first devices to be invented in this era were fashioned out of biologically inert plastics made possible by the advances in polymer chemistry, which allowed the device to be stretched into a linear configuration for insertion and regain its shape once in the uterine cavity. Different shapes and sizes of inert devices were tried and after improvements in methods of evaluation it was found that larger devices, while appearing to be more effective in preventing pregnancy than smaller ones and less likely to be expelled, produced higher rates of side effects such as cramping and bleeding and therefore had higher rates of medical removal (Tatum 1989). The addition of copper wire allowed a reduction in the size of the plastic frame and resulted in lower rates of adverse side effects without compromising efficacy. By increasing the amount of copper in the device lower pregnancy rates

have been achieved and the newer high copper load IUDs have proved to be highly effective (Treiman 1995). However, problems of expulsion, pain and bleeding remain (Treiman 1995).

The development of a reliable anchoring technology in 1985 meant that the plastic frame could be completely dispensed with (Wildemeersch 1988). The frameless IUD consists of six copper cylinders, each 5 millimetres long and 2.2 millimetres wide, on a nylon thread, which has a knot at one end that is implanted into the fundal myometrium to a depth of one centimetre. The surface area of copper is 330 square millimetres. After reports of excessive early expulsions, the introducer for the frameless IUD was changed for the marketed device, GyneFix.

It is claimed that it is the frame of the traditional IUD that is responsible for the expulsions, pain and bleeding and that the frameless device minimises these problems (Van Kets 1997). This review assesses these claims.

OBJECTIVES

To determine whether the frameless IUD is superior to the classical framed devices. We wished to test the hypotheses that compared to framed devices the frameless device:

- 1) has a lower pregnancy rate,
- 2) has a lower expulsion rate,
- 3) is associated with less pain

- 4) is associated with less bleeding,
- 5) has a similar risk of pelvic infection.

METHODS

Criteria for considering studies for this review

Types of studies

A trial was eligible for inclusion if the comparison groups were created by a randomisation procedure.

Types of participants

Women requesting an IUD for contraceptive purposes.

Types of interventions

Frameless IUD or any classical IUD with a copper bearing frame.

Types of outcome measures

Pregnancy rate, ectopic pregnancy rate, expulsion rate, removal rate for pain, for bleeding, for pain and/or bleeding and pelvic inflammatory disease rate, continuation rate.

Search methods for identification of studies

The frameless IUD has appeared in three forms, FlexiGard, Cu-Fix and GyneFix and the search was based on these terms. No methodological filters were used. We searched the Cochrane Controlled Trial Register (Cochrane Library Issue 2, 2004), MEDLINE (Jan 1980 to Mar 2004), EMBASE (Jan 1985 to Dec 2000), POPLINE (Jan 1980 to Mar 2004).

Electronic search strategy (Ovid):

- 1) GyneFix.tw
- 2) FlexiGard.tw
- 3) CuFix.tw
- 4) Cu-Fix.tw
- 5) Copper-Fix.tw
- 6) or/1-5
- 7) intrauterine devices (MESH)
- 8) frameless.tw
- 9) 7 and 8
- 10) 6 or 9

Reference lists from identified studies and reviews of IUD performance were examined for relevant studies. Authors and the manufacturer of the frameless device were contacted for any unpublished studies.

Data collection and analysis

Abstracts of trials identified by the search strategy were scrutinised by the first author to see whether they satisfy the inclusion criteria, and we obtained photocopies of those considered relevant. We independently abstracted data from each included article onto a data abstraction form, and resolved any discrepancies by discussion. We requested additional information about the included studies from the authors as necessary.

We screened the trials included in the review for the following features, using a pre-specified data extraction form for:

Trial design and characteristics:

- 1) unit of randomisation,
- 2) generation of allocation sequence,
- 3) allocation concealment,
- 4) mechanism of blinding of treatment to participants, investigators, outcome assessors and data analysts,
- 5) evidence of a power calculation,
- 6) single or multicentre design,
- 7) location, duration and timing of the trial,
- 8) numbers excluded from analysis and reasons,
- 9) statistical methods used to calculate cumulative rates
- 10) source of funding,
- 11) consumer involvement.

Baseline characteristics of participants:

- 1) number,
- 2) age,
- 3) parity,
- 4) recent pregnancy,
- 5) regular menstrual cycle,
- 6) sexual activity,
- 7) history or evidence of past pelvic infection or infection with chlamydia or gonorrhoea,
- 8) presence of uterine fibroids,
- 9) previous contraceptive usage.

Intervention:

- 1) IUD type,
- 2) insertion technique,
- 3) training of inserters,
- 4) duration of treatment.

Outcomes:

- 1) cumulative expulsion rates, early within 2 months of insertion, and subsequent,
- 2) cumulative and annualised pregnancy rates,
- 3) pregnancy rates with device in-utero and after expulsion,
- 4) cumulative ectopic pregnancy rates,
- 5) miscarriage rate,
- 6) cumulative and annualised removal rates for pain, bleeding, pain and/or bleeding,
- 7) cumulative and annualised pelvic inflammatory disease rates,
- 8) insertion failure rates,

- 9) perforation rates,
- 10) numbers completing interval,
- 11) women-years of experience,
- 12) method to diagnose pregnancy.

Assessing methodological quality:

The first author assessed the quality of the included studies. Control of selection bias was assessed by the methods used to generate and conceal the allocation sequence. Ascertainment bias was evaluated by the masking methods used in the trials. Quality was also judged on loss to follow-up rates.

Statistical analysis:

Survival (time-to-event) methods are used in contraception studies that involve long periods of observation and take into account varying lengths of time that women remain in a study. Kaplan-Meier or daily life-table estimates are commonly used in IUD studies (Farley 1986). Monthly (actuarial) life-table estimates have also been used extensively in the past (Tietze 1973). Farley has shown that the results obtained are very similar (Farley 1986) and for the purposes of this review are treated the same and combined in the meta-analyses. Both methods give estimated probabilities of event over a specific time period, which are expressed as percentages or rates per 100 women.

In IUD studies reasons for discontinuation 'compete' with each other in the sense that if a woman discontinues from the study because the IUD is expelled, for example, or because of excessive bleeding, she is no longer at risk of pregnancy in that interval. Based on how these competing events are handled, two types of rates can be derived in life-table analysis in contraception studies. Most studies report adjusted, or non-competing single decrement life-table rates, in which the rates are calculated after adjusting (censoring) for discontinuations for other reasons (also called cumulative 'net' probability rates by statisticians (Farley 1986), and 'gross' cumulative rates by demographers (Tietze 1973)). Adjusted rates are theoretical and not observable, and provide a pure estimate for each reason for comparison with other IUDs. The advantage of the adjusted rate is that an excess rate for one reason, for example expulsion, will not influence discontinuations rates for other reasons. Adjusted rates are used when looking at single events, such as pregnancies or expulsions, in isolation to compare events rates among different devices, as the influence of other events, such as discontinuations for bleeding, is removed.

Crude rates, or competing multiple decrement life-table rates, on the other hand, are discontinuation rates for an event without adjusting for other events (also called 'net' rates by Tietze). Crude rates provide an estimate of overall IUD performance, showing the relative importance of different reasons for discontinuation, which are additive. Crude rates give systematically lower estimates. The preference for adjusted, single decrement, non-competing methods has been re-evaluated recently, and it has been argued that crude rates, as cumulative incidence rates, are more appropriate for IUD studies (Tai 2001). Farley *et al* have argued that adjusted rates are more appropriate when estimating the effectiveness of a

contraceptive method, but that cumulative incidence estimates are more appropriate when making programmatic decisions regarding contraceptive methods. This review uses the published adjusted, single decrement, non-competing life-table rates for comparing the discontinuation rates among devices (Farley 2001).

The effect measures reported in this review are rate ratios and rate differences. Rate ratios are calculated by dividing the adjusted life-table rates for the frameless device by the rates for the control device. The variance and 95% confidence intervals for the rate ratios are calculated using the Taylor series method described by Kleinbaum *et al* (Kleinbaum 1982). When Kaplan Meier (daily) or monthly life-table rates, and the standard errors, were not available we used the ratio of Pearl rates (rate per 100 women-years of use). We also used this method when there were no events with the experimental or control devices, by adding half to each event cell, as it is not possible to calculate a rate ratio using life-table rates with zero events. Using data from the WHO study in this review, we have shown the ratios of adjusted, single decrement life-tables and ratio of Pearl rates are similar, permitting their combination in meta-analysis (O'Brien 2004a). We calculated the variance and 95% confidence intervals for individual trials using the method described by Hasselblad *et al* (Hasselblad 1995). The null value (no difference) for rate ratios is one. When the confidence interval includes one there is no statistically significant difference between the devices. Rate ratios estimate the relative values of IUDs, and are dimensionless.

Rate differences tell the magnitude of the difference in performance, and are calculated by subtracting the cumulative life-table rate for the control device from the rate for the frameless device, and are expressed as events per 100 women. When the rate with the frameless device is lower the results takes a negative sign in this review. The null point for the rate difference is zero, so when the confidence interval straddles zero there is no statistical difference between the devices.

To combine the studies we used the inverse variance method, after logarithmic transformation for the summary rate ratio, as described in the Cochrane Reviewers Handbook (Deeks 2004), where the individual effect sizes are weighted according to the reciprocal of their variance. The fixed effect model was used for all meta-analyses. The meta-analyses were tested for heterogeneity. Only studies that are statistically homogeneous are combined. We used Microsoft Excel for the calculations.

The prototype inserter used in the early frameless device (Cu-Fix and FlexiGard) was associated with a high rate of early expulsions and pregnancies in the WHO (Rowe 1995) and Rosenberg (1996) trials. This review is primarily interested in the performance of the marketed device, GyneFix with a different introducer. Because of the possible clinical heterogeneity introduced by the type of inserter used, we analysed the WHO and Rosenberg studies separately from the other trials when performing the meta-analyses of expulsions and pregnancies. First year events are carried forward into subsequent years in cumulative rates. Discontinuation

for pregnancies and expulsions in subsequent years, however, can be isolated from first year events by looking at annual events after the first year, or cumulative rates beginning at the second year of use. As the frameless device itself used in the four trials is identical (D Wildemeersch, personal communication), we assumed that among women who retained the device, the discontinuation rates for other events are not influenced by the inserter used, and therefore that data from the WHO and Rosenberg trials can be combined with the GyneFix trials for these events at all time periods.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Seven studies were identified and four were included (Rowe 1995, Rosenberg 1996, Wu 2000, D'Souza 2003). See Table of Included Studies.

Interim three-year data from a WHO trial have been published which used 30th September 1994 for the cut-off date for life-table rates (Rowe 1995). The authors have provided us with eight-year data, cut-off at 31st December 1999. In the WHO trial there was a substantial reduction in the number of women who entered and completed the seventh year of observation (60% for the frameless and 50% for TCU380A). As inclusion of the later data might introduce bias, results are analysed to six years only. A Chinese study is ongoing; 3 year data have been published (Wu 2000). The authors provided unpublished data to 3 years. The report by Wu (Wu 1998) is the first year data from this trial.

Three Chinese studies were excluded. See Table of Excluded Studies. One was conducted in two phases, 1990/91 (199 insertions) and 1995 (114 insertions). FlexiGard was used in the early period and GyneFix later. This trial was excluded as the data from the early phase is already included in the WHO trial (Tianjin centre) (Cao 2000). Another report (Hui-Qin 1999) describes the six-year experience in one centre, Shanghai, of the WHO multicentre trial and is included in the six-year data for the latter. One Chinese trial (Dou 2001) was excluded because a proportion of the participants were not randomised. Although described as randomised, if participants did not want the device allocated they were allowed to choose the alternative and were included in the analysis (Dou, personal communication).

The number of participants in the included studies varied from 4,337 in the WHO trial, which is the largest IUD trial in the world literature, to 175 in the DSouza trial. The total number of women in the trial was 5,939, accounting for 23,180 years of use. Three trials were multicentred: WHO trial (Rowe 1995) in 13 developing and transitional countries, Rosenberg (1996) in North

America and Europe, Wu (2000) in 6 centres in China. All the trial enrolled women for routine contraception, except the DSouza (2003) study in which the devices were inserted for emergency use, but also intended for use long-term. The latter trial was designed to compare pain and ease of fitting, and pain and bleeding in the 6 weeks of follow-up. The three main trials excluded women who had not had children (Rowe 1995, Rosenberg 1996, Wu 2000), TCU380A is the comparator in three of the trials (Rowe 1995, Rosenberg 1996, Wu 2000), and TCU380 Slimline in one trial (D'Souza 2003), a device that is structurally similar, and performs very similarly, to TCU380A (O'Brien 2004b). The two early trials use a prototype inserter for the frameless device called FlexiGard in Rowe 1995, and Cu-Fix in Rosenberg 1996. However, the inserted device used in all the trials is identical (Wildemeersch, personal communication).

The WHO trial had a pilot phase involving 40 insertions in each of the 28 centres, accounting for a quarter of all insertions (Rowe 1995). Six centres did not proceed into the main phase because of poor results in one centre, and failure to adhere to the protocol in the other five centres. However, as the results in the pilot phase were similar to the main phase, all the data from the pilot were included in the analysis. The decision in the WHO trial to include the results from the pilot phase in the analysis seems reasonable.

Adjusted, single decrement methods were used in the three long-term trials to calculate the cumulative discontinuation rates; Kaplan Meier methods were used in the WHO and Wu trials, and Rosenberg used the monthly life-table method. Rosenberg used the crude multiple decrement life-table method to calculate the continuation rates. The latter is not used in this analysis.

Rowe (1995) was funded by WHO, the Rosenberg trial (1996) by GynoPharma which manufactured TCU380A, and the Wu study was funded by Control Europe nv/sa, the manufacturers of the frameless device GyneFix. Control Europe partially funded the DSouza trial (2003).

Risk of bias in included studies

A computer generated randomisation sequence was reported in the WHO and Wu studies (Rowe 1995, Wu 2000), and random sampling tables in DSouza (D'Souza 2003). All three used sealed envelopes to conceal upcoming allocation. The Rosenberg trial also used a computer generated allocation sequence (Rosenberg 1996). However, allocation concealment is less clear in this trial, which used block sizes of four and no information is given on whether the blocks were permuted or the approach used to randomly select the blocks. The inadequate generation process could subvert randomisation. In the absence of masking, with block sizes of four, many future assignments will be accurately predicted from the past assignments.

It appears that no attempt was made to blind the participants to the device used in any of the trials, except in the DSouza study in which the patients were blinded to the type of the device, and the assessor

at follow-up in 88% of cases. Ascertainment and management biases are possible in all of the trials, although least likely in DSouza trial.

A large number of randomised women (115 of 989) were excluded in the analysis in the Rosenberg trial. The majority (87) were from six centres, data from which were excluded because of protocol violations, mainly because the reason for termination was not recorded. As all women in the centres were excluded, this is not likely to have biased the outcome of the trial. There were no reported exclusions in the WHO and Wu trials.

The losses to follow-up rates were also higher in the Rosenberg trial; at two years 16% of women randomised to Cu-Fix and 18% of women randomised to TCu380A. This corresponds to cumulative loss to follow-up rates of 26.7% and 23.7% respectively. These differences were not statistically significant. The two-year loss to follow-up rate in the WHO trial was close to 6% in both arms, and at six years the losses were 10.3% and 11.6% in the frameless and TCu380A arms respectively. Only two women were lost to follow-up in the Wu trial, one in each arm of the trial.

Effects of interventions

Insertion Failures

Problems with inserting the frameless device were reported in three trials. In the Wu study (Wu 2000), there was only one insertion failure in the GyneFix group, and none with TCu380A group, and one in the DSouza (D'Souza 2003) trial. The summary relative risk of insertion failure with GyneFix was 2.94, 95% confidence intervals 0.31 to 28.04. There were 53 of 2155 insertion failures with the frameless device and one with TCu380A in the WHO trial (Rowe 1995). Rosenberg (Rosenberg 1996) did not report any failed insertions with the similar device. However as there

was no mention of training of inserters, it was a multicentre trial, the device was not in general use, and the expulsion rate in the frameless arm was double that in the WHO trial, underreporting of insertion failures is a possibility.

Expulsions

First year expulsions with GyneFix in the Wu trial were 40% lower than with TCu380A but the difference was not statistically significant (RR 0.57, 95% CI 0.24 to 1.35) (Wu 2000). Eight of 302 (2.6%) inserted GyneFix devices were expelled in the first year as against 14 of 305 (4.6%) TCu380A IUDs. The expulsions rate in the other two trials, which used a different inserter, was higher with the frameless device. First year expulsion rates for the frameless and control devices were 6% and 3% in the WHO trial (Rowe 1995), and 10% and 2% in the Rosenberg trial (Rosenberg 1996), and by the end of the first year the summary expulsion rate in these two trials was more than double with the frameless device (RR 2.48, 95% CI 1.89 to 3.26).

The WHO and DSouza trials were the only ones to compare expulsions occurring less than 12 months after insertion; 51% of 141 expulsion in three years with FlexiGard occurred in the first 90 days as against 22% of 87 with TCu380A (Rowe 1995). The rates were similar in the small DSouza trial. In the Wu trial, the authors note that four of eight expulsions of the frameless device in the first year occurred in the first three months after insertion. By the end of the third year in the Wu trial there was a statistically significant 60% reduction in expulsions with the frameless IUD (RR 0.41, 95% CI 0.19 to 0.87). The absolute reduction in expulsions was around 4 per 100 women and this difference was also significant (RD -4.38%, 95% CI -7.91 to -0.85). The cumulative expulsion rate in the WHO trial at three years continued to be greater with the frameless device (RR 1.75, 95% CI 1.29 to 2.32; RD 3.00, 95% CI 1.47 to 4.53) (Table 1).

Table 1. Cumulative expulsion rates at 3 years

Study	Frameless	TCu380A	Rate Ratio	Rate Difference
	Rate (SE)	Rate (SE)	RR (95%CI)	RD (95%CI)
Rowe 1995	7.1 (0.6)	4.1 (0.5)	1.73 (1.29 to 2.32)	3.00 (1.47 to 4.53)
Wu 2000	3 (0.98)	7.38 (1.51)	0.41 (0.19 to 0.87)	-4.38 (-7.91 to -0.85)

The cumulative expulsion rates for the three trial are heterogeneous at one, two and three years ($p < 0.0005$) and were not combined, as the difference among the results of the studies is likely to be due to clinical heterogeneity rather than chance.

As insertion-related problems are unlikely to have an effect beyond the first year, the ratios of annual expulsion rates from the WHO and Wu trials, which were homogeneous, were combined in meta-analyses up to three years. Using person-time data the combined

ratios from these two trials were similar in the second (RR 0.69, 95% CI 0.34 to 1.37) and third years (RR 0.94, 95% CI 0.46 to 1.91). These data were not available for the Rosenberg trial.

The WHO trial was the only one with long-term data. The annual net expulsion rates were similar after the first year. The cumulative net expulsion rates from years two to six, i.e. those who remained in the study after one year, were similar; 3.1% with FlexiGard and

2.6% with TCU380A (RR 1.20, 95% CI 0.79 to 1.84).

The rate of expulsion in the control device, TCU380A, was much higher in the Wu trial than in the earlier trials. The cumulative rate at two years was 2.0% in the Rosenberg trial, 3.4% in the WHO trial, and almost double in the Wu trial at 6.3%.

Pregnancies

The cumulative pregnancy rates in the Wu trial (Wu 2000) were similar with both devices, with just one pregnancy in all, which occurred during the first year with TCU380A, giving a non-significant cumulative rate difference of less than 1 per 100 women at 3 years (RD -0.34, 95% CI; -1.01 to 0.33).

The pregnancy rate with the frameless IUD in the WHO trial (Rowe 1995) at the end of the first year was twice that with the control device, although not significantly (RR 2.00, 95% CI 0.88 to 4.53). The Rosenberg trial (1996) did not provide enough data to incorporate into a meta-analysis of rate ratios but the combined absolute rate difference for the WHO and Rosenberg trials was less than 1 per 100 women at one year (RD 0.71, 95% CI 0.10 to 1.31). By the end of the second year the pregnancy rate with the frameless device was 60% higher than with TCU380A (RR 1.61, 95% CI 0.90 to 2.87), but remained non-significant.

When we combined the cumulative results for the three trials there was a tendency towards a higher pregnancy rate with the frameless device at one year (RR 1.79, 95% CI 0.81 to 3.95) to three years (RR 1.34, 95% CI 0.85 to 2.10), but the difference was never statistically significant (Table 2). The trials were statistically homogeneous at each interval.

Table 2. Pregnancy rate at 3 year

Study	Frameless	TCu380A	Rate ratio	Rate difference
	Rate (SE)	Rate (SE)	RR (95%CI)	RD (95%CI)
Rowe 1995	2.2 (0.3)	1.6 (0.3)	1.38 (0.87 to 2.17)	0.60 (-0.23 to 1.43)
Wu 2000	0.0 (0.0)	0.3 (0.3)	0.32 (0.01 to 7.91)	-0.34 (-1.01 to 0.33)
SUMMARY			1.34 (0.85 to 2.10)	0.03 (-0.49 to 0.55)

When we looked at events distant from insertion, isolating the effects of early expulsions, the frameless device had a lower pregnancy rate. The cumulative rate in the WHO trial from years two to six was 1.2% with FlexiGard and 2.3% with TCU380A, a difference that was statistically significant (RR 0.53, 95% CI 0.32 to 0.91) but clinically small. The rates for the whole six years were similar, 2.4% and 2.8% respectively (RR 0.86, 95% CI 0.56 to 1.32).

Ectopic Pregnancies

The proportion of pregnancies that were ectopic was lower with the frameless device in the WHO trial; 1 of 42 pregnancies at six years with FlexiGard was ectopic and 7 of 46 with TCU380A (p=0.03) (Rowe 1995). However, the overall rate of ectopic pregnancies was very low with both devices, and were never statistically different; the cumulative rate in the WHO trial at six years was only 0.06% with the frameless device and 0.46% with TCU380A (RR 0.20, 95% CI 0.02 to 1.65). There were no ectopic pregnancies reported in the Rosenberg trial and the one pregnancy in the Wu trial was intrauterine.

Pain and/or Bleeding

When we examine together all removals for reasons of pain and/or bleeding there was a tendency in individual studies for reduced removals with the frameless device in the first, but reaching statistical significance in the second year only (RR 0.76, 95% CI 0.60 to 0.97). In subsequent years there was no statistical difference between the removal rates. At the end of the third year the combined results for the WHO and Wu trials were similar (RR 0.92, 95% CI 0.74 to 1.14) (Table 3). At six years in the WHO study the discontinuation rate was 13.1% for the frameless device and 11.6% for TCU380A (RR 1.13, 95% CI 0.93 to 1.37).

Table 3. Discontinuations for pain and/or bleeding at 3 years

Study	Frameless	TCu380A	Rate Ratio	Rate Difference
	Rate (SE)	Rate (SE)	RR (95%CI)	RD (95%CI)
Rowe 1995	7.1 (0.6)	7.5 (0.6)	0.95 (0.75 to 1.19)	-0.40 (-2.06 to 1.26)
Wu 2000	4.5 (1.2)	6.3 (1.4)	0.72 (0.36 to 1.44)	-1.77 (-5.45 to 1.91)
SUMMARY			0.92 (0.74 to 1.14)	-0.63 (-2.15 to 0.88)

Bleeding Alone

Only two trials (Rowe 1995) and (Wu 2000) reported removal rates for bleeding separate from pain. At no time in either of the trials, individually or combined, was there any statistical significant difference in the cumulative rates between the devices, apart from the sixth year in the WHO trial when the frameless device had an excess cumulative removal rate for bleeding, which just reached statistical significance (RR 1.29, 95% CI 1.01 to 1.65) (Rowe 1995).

Pain Alone

The same two trials also reported separate results for removals because of pain alone, a reason cited much less frequently than bleeding. In the first year the combined removal rates for pain were similar (RR 0.83, 95% CI 0.40 to 1.72). In subsequent years there tended to be fewer removals for pain with the frameless device, but the rate ratio reached statistical significance in the second year only, and the rate difference in the second and third years only. At the end of the third year (WHO and Wu trials combined) there was a non-significant 40% reduction in removals (RR 0.60, 95% CI 0.34 to 1.05). This translates into a rate difference of less than 1 per 100 women (RD -0.82, 95% CI -1.51 to -0.13) (Table 4). By the end of the sixth year in the WHO trial the results had not changed appreciably (RR 0.68%, 95% CI 0.43 to 1.06; RD -1.00, 95% CI -2.11 to 0.11). DSouza reported a lower rate of removals for pain in the first 6 weeks of use with GyneFix, but the rate with TCU380S was unusually high at 7 of 82 insertions (8%) in this brief study (D'Souza 2003).

Table 4. Discontinuations for pain at 3 years

Study	Frameless	TCU380A	Rate Ratio	Rate Difference
	Rate (SE)	Rate (SE)	RR (95%CI)	RD (95%CI)
Rowe 1995	1.2 (0.3)	1.9 (0.3)	0.63 (0.35 to 1.13)	-0.70 (-1.53 to 0.13)
Wu 2000	0.0 (0.0)	1.1 (0.6)	0.14 (0.01 to 2.67)	-1.08 (-2.30 to 0.14)
SUMMARY			0.60 (0.34 to 1.05)	-0.82 (-1.51 to -0.13)

Pelvic Inflammatory Disease

The WHO and Wu trials provide discontinuation rates for pelvic inflammatory disease. There were no removals in the Chinese trial and a very low rate with either device in the WHO trial (0.1% with the frameless and 0.4% with TCU380A at three years), with no statically significant difference between the devices (RR 0.80, 95% CI 0.23 to 2.81).

Apart from the single perforation with GyneFix in the DSouza trial, there were no other perforations in three trials that reported this outcome, in a total of 5,065 insertions with either device. This outcome was not reported in the Rosenberg trial.

Perforations

Continuations

The continuation rates with the frameless device in the WHO trial tended to be lower than for the control device, although, apart

from the first year, did not reach statistical significance throughout the six years (Rowe 1995). The difference was mainly due to excess expulsions with the frameless device in the first year. The rates were 84% and 87% for the frameless and control devices at the end of the first year (RR 0.97, 95% CI 0.94 to 0.99; RD -2.80, 95% CI -4.88 to -0.72), 72% and 73% by the third year (Table 5), and 58% and 60% at the end of the sixth year (RR 0.97, 95% CI 0.92 to 1.02, RD -2.08, 95% CI -5.09 to 0.93). In the Wu trial the continuation rates were higher with both devices than in the WHO trial. In this trial the rates tended to be higher with GyneFix, significantly in the second and third years. Here too the difference in continuation rates is explained mainly by the difference in expulsions, which were lower with the frameless device. At the end of the first year the rates were 95% with GyneFix and 92% with TCu380A (RR 1.04, 95% CI 1.00 to 1.08; RD 3.56, 95% CI -0.33 to 7.45). By the end of the third year the corresponding rates were 91% and 85% (RR 1.06, 95% CI 1.00 to 1.13; RD 5.48, 95% CI 0.33 to 10.63) (Table 5). The Rosenberg trial reported only multiple decrement data for this outcome.

Table 5. Continuation rates at 3 years

Study	Frameless	TCu380A	Rate Ratio	Rate Difference
	Rate (SE)	Rate (SE)	RR (95%CI)	RD (95%CI)
Rowe 1995	71.8 (1.0)	73.0 (1.0)	0.98 (0.95 to 1.02)	-1.24 (-3.94 to 1.46)
Wu 2000	90.7 (1.7)	85.3 (2.0)	1.06 (1.00 to 1.13)	5.48 (0.33 to 10.63)

DISCUSSION

The frameless IUD has been assessed in four trials, one of which, the WHO trial, was the largest IUD trial to date involving over 4,000 women with followed-up data for eight years (Rowe 1995). Fortunately the frameless device has been compared in each trials with one of the best performing IUDs in current use, TCu380, so its place in contraceptive practice can be assessed. The assessment, however, is complicated by the fact that the WHO and Rosenberg (1996) trials used an inserter for the frameless IUD which proved to be deficient and was associated with a significantly higher early

expulsion rate, and consequently, pregnancy rate. When the original inserter was used the expulsion rate was twice that with the traditional framed device. The pregnancy rate was also greater, although less so.

The inserter was modified for the marketed device, GyneFix, and early expulsion data which are clinical useful can be assessed in the sole long-term trial that used this inserter (Wu 2000). The expulsion rate in this small trial tended to be lower with the frameless device, though not significantly better than TCu380A at one year. The other GyneFix trial (D'Souza 2003) was of too short a duration to give useful information on expulsions. In the partially randomised trial by Dou et al only 2% of around 1,800 insertions ended in expulsion, with a similar rate with both GyneFix and

Multiload 375 (Dou 2001).

When we combined studies for events distant to insertion we found that expulsion rates beyond the first year were similar; they were rare with both devices. Annual expulsion rates in years two and three were similar, as were cumulative rates for years two to six in the WHO trial. The evidence suggests that if the frameless device is correctly sited expulsion are rare, though not clearly superior to TCU380A. It was hoped that the anchoring technology in the frameless device would improve the retention of the device. This has not been borne out in the trials for expulsions after the first year, although only a minority of expulsions occur then.

The relationship between an IUD and early expulsions is confounded by the performance of the clinician inserting the device. Improved rates of early events, expulsion and pregnancy, between studies may be due to improvement in the IUD or better inserter's skills. While the improved retention rates with the frameless device in the Wu trial has been attributed to the new inserter (Wu 2000), this is difficult to confirm. The skill of the clinician inserting the device would appear to have played a large part in the excess expulsions with the frameless IUD in the WHO trial.

Because of the important role of the skill of the clinician it is difficult to assess, in the one long-term trial with GyneFix, whether it was the new inserter or the skill and experience of the Chinese clinicians, who had previous experience with the frameless device, which resulted in an improved retention rate with the newer inserter. However, the good retention rate in the Wu trial has been replicated in Dou trial (2001). Only 21 of 980 GyneFix devices were expelled (2.1%), similar to the performance in the Wu trial (8 of 302, 2.6%). However, a number of studies found very low expulsion rates with the original introducer. Hui-Qin et al had no first year expulsions in 100 insertions (Hui-Qin 1999), and Batar et al reported an expulsion rate of only 1.5% at one year with the prototype inserter in 344 women (Batar 1992). These rates are lower than the 2.6% found with the newer inserter for GyneFix in the Wu and Dou studies.

A retrospective case series from a specialist centre suggests that the problem of early expulsions continues (Dennis 2001). Sixty eight of 1000 devices (7%) were known to be expelled in the first year, in opportunistic follow-up. Two thirds of the insertions were by practitioners who had experience with GyneFix, but their expulsion rate was no better than that for the less experienced. In this setting, experience did not resolve the problem of expulsions with GyneFix. In another retrospective review of 138 GyneFix insertions with limited follow-up, 8% of devices were expelled in the first year, one half in the first two months (Geyoushi 2002).

Failure to implant the device is sometimes evident at the time of insertion. In the two GyneFix trials, the failed insertion rates were very low and there was no statistically significant difference between the devices. A new introducer (Mark 2) for GyneFix has been developed to simplify insertion. It is too early to say if this will

overcome the problems in implanting the device. Some clinicians report having less success with the new inserter (Brockmeyer 2004, Wildemeersch 2004).

The retention of frameless device appears to be dependent on the skill and dexterity of the clinician inserting the device, whether with the original inserter, or with the first and probably the latest (Mark 2) inserter for GyneFix.

Expulsions that are unrecognised are an especial concern as pregnancy will be more likely. The small size of the frameless device allows it to be expelled sometimes without the women being aware of it. In the WHO (1995) trial at three years (cut off Sept 1994) the unnoticed expulsion rate (16/35) was three times that with TCU380A (4/28). In a UK report four of 16 expulsions were unnoticed, two of which resulted in pregnancy (Masters 2000), and in another 4 of 11 were unnoticed (Geyoushi 2002). On the other hand, unrecognised partial expulsions, which may be more frequent with TCU380A, could be equally hazardous. In the Wu trial 18 of 22 expulsions with TuCu380A were partial as against 1 of 9 with GyneFix.

Not surprisingly, the WHO and Rosenberg trials showed an excess pregnancy rate with the frameless device in the first year, reflecting the higher early expulsion rate. But the frameless device performed better in subsequent years. A frameless IUD which has been retained beyond the first 12 months appears to be highly effective, indeed more so than TCU380A. The cumulative pregnancy rate for years two to six was halved with the frameless compared with the TCU380A devices, although the reduction in pregnancies in the five years amounts to only 1 per 100 women. This compensated for the early excess pregnancies and interestingly occurred despite the slightly higher expulsion rate with the frameless device. Any excess in pregnancies due to unnoticed expulsions with the frameless device was not apparent in the data.

In the Wu trial using GyneFix, the problem of early expulsions with the frameless device was avoided and there were no pregnancies in the 870 women-years of experience over three years. However, the TCU380A had just one pregnancy with a similar exposure. In the Dou study likewise, the proportion pregnant at one year (0.4%) was very low in both the GyneFix and Multiload 375 arms.

Ectopic pregnancies are rare with all high load copper IUDs including the devices in this review. In the WHO trial the cumulative rate with the control device, TCU380A, was less than one per 100 women at six years but even lower with the frameless device, although this difference did not reach statistical significance.

It was hoped that the introduction of a frameless device would reduce or eliminate the problems of bleeding and pain associated with IUD use. This however has not been realised. The removal rates for bleeding, and for pain and/or bleeding, were similar. This review found some evidence, however, that women might experience less pain with the frameless device, although this tendency

did not reach statistical significance when compared to TCu380A. In the partially randomised trial by Dou (2001), there were fewer removals for pain with the frameless device. This potential benefit may be more relevant for nulliparous women, but the only randomised long-term data comes from trials that included only parous women. However, pain in the absence of bleeding is an unusual reason for discontinuation.

Removal for excessive bleeding occurs when the degree of bleeding is intolerable. An IUD associated with a smaller increase in menstrual bleeding could still be clinically useful, even if this had little impact on removal rates. Two studies have compared the blood loss in women randomised to the frameless device or TCu380A, part of the large WHO trial. The Brazilian trial involved 40 women (Andrade 1993). There were 80 women in a Chinese trial but data on only a subgroup with 'normal' menstrual blood loss (20-80 mls), is available, 25 women using the frameless device and 24 women with TCu380A (Wu Shangchun, personal communication). Our meta-analysis using the weighted mean difference in blood loss at each of the intervals three, six, 12 and 24 months, shows no consistent pattern. The mean blood loss pre-insertion, and after, was about double in the Chinese compared to the Brazilian women.

The evidence lends little support to the proposition (Wildemeersch 1999) that it is the frame in modern small-framed IUDs which is responsible for symptoms of bleeding and pain. Rather, it seems likely that the copper in IUDs is the main factor, although it is possible that even the small volume of the flexible frameless device also plays a part. A recent meta-analysis comparing IUDs with identical frames but different copper loads, found that high copper-load devices had a 20% higher cumulative removal rate for bleeding and pain the end of the first and second year of use, although no difference by the end of the third year (O'Brien 2004c). A new frameless IUD, GyneFix (Mini), has been introduced with four instead of six copper cylinders. The total copper surface area has been reduced to 200 cubic millimetres and the length to 2 cm (Cao 2004, Sivin 2004, Wildemeersch 2004). The smaller device has not been evaluated in randomised trials.

The continuation rates with both devices in both the WHO and Wu trials were good. The difference in continuation rates between devices was largely due to higher expulsion rates with the frameless device in the WHO trial.

The difference between routine use and clinical trials is also evident in the perforation rate. There was just one reported perforation with the frameless device in around 3000 insertions in the four trials in this review, and none with the framed device. In a case series from Belgium, seven perforations were reported in the first 5,000 GyneFix insertions (Vekemans 1999). There have been anecdotal reports of perforations with GyneFix into the bladder (Eskandar 2003), anterior abdominal wall (Aust 2003) and bowel (Reuter 2001). It is unknown whether the perforation rate dif-

fers from that with framed devices. A review in Sweden of IUD perforations has recommended an anonymous national register of perforations (Andersson 1998). Such a register would be valuable in monitoring serious adverse effects when new devices are introduced.

Anecdotal reports suggest that greater precision in GyneFix insertion is achieved when the woman is in the lithotomy position, and the manufacturer recommends this position. There may be some latitude in the position of framed IUDs as they may accommodate in their position during the first three months of use (Faundes 2000). This is not the situation with the frameless device, which needs to be implanted with precision into the myometrium. The general difficulty in precisely measuring the length of the uterus at sounding may compound the situation. An error either way risks expulsion or perforation.

The relatively small diameter of the frameless device (3.8 mm) at insertion may also make it more suitable for post-coital use than a larger framed device in terms of ease of insertion and discomfort caused. The DSouza trial compared the insertion-linked pain, and pain and bleeding in the following six weeks in women who had a GyneFix or TCu380S inserted for emergency contraception. Around 80% of 175 women were nulliparous. Pain at insertion was greater with the frameless device, although there was less pain during the subsequent 6 weeks in GyneFix users. There was no difference in the ease of insertion.

The anchoring technology may offer particular advantages in situations where there may be a higher risk of expulsions with a classical IUD, such as a distorted uterine cavity, repeated expulsions of a classical device, or post placental insertion (Van Kets 1997). However, there are no randomised studies of GyneFix in these situations.

It is difficult to assess whether it is intrinsically more difficult to correctly fit a frameless device. Adequate training of clinicians may be particularly important when introduced to the insertion technique. It requires new skills, not least competence in puncturing the myometrium to the correct depth, a procedure which clinicians studiously avoid when inserting other devices. Retraining service providers in the new insertion technique is expensive. The frameless device is also more expensive than TCu380. Family planning programmes have to consider whether any potential benefits from GyneFix outweigh the extra resources required for retraining and monitoring performance.

Some authors have suggested that if there is any doubt about the quality of the insertions an ultrasound scan should be performed. This could also be recommended for clinicians learning the new insertion technique. However, this facility will not be available in most clinic settings. A careful audit of early expulsions is important for clinicians in training.

An assumption running through the meta-analysis in this review

is that events after one year of use are not affected by the problem related to insertion - as long as the device remains in situ it does not cause other insertion related problems. While this is likely to be valid, there is not way of testing it in the data. Another assumption, when analysing early pregnancy and expulsion rates, is that the modified inserter in GyneFix warrants separate analysis from trials using the original inserter. While the data in this review suggests that this may be appropriate, other trials with GyneFix are necessary to confirm this approach.

Empirical evidence shows that inadequate or unclear allocation concealment tends to introduce selection bias, which in general favours the experimental treatment, more so in unblinded studies (Schulz 1995). Allocation concealment, unlike masking, is always possible. The three trials examined in this review suffer from weaknesses in reported concealment of the upcoming allocation. This is especially true for the Rosenberg trial.

In the DSouza trial the patients were blinded to the device inserted, and assessment at follow-up was blinded in 88%. No attempts were made to blind any of the participants in the other trials, and the absence of masking could have influenced the outcome. This allows a management bias where women are treated differently in the knowledge of which IUD they are using. For example, medical therapy, or hopeful expectation, may be more likely to be used, and for longer, in women with the new device, if it is thought that this device produced less pain or bleeding, thereby delaying the removal for these symptoms. This could explain the early tendency towards fewer early removals for bleeding and/or pain with the frameless device found in this meta-analysis, but which was abolished by the end of the third year. More thought needs to be given to the possibilities for blinding in IUD trials. Logistical reasons may make this difficult as the clinician providing the care can usually identify which device is being used by the threads seen at assessment. Attempts have been made in at least two other randomised trial of TCu380A to mask the participants to the device inserted. In one 'records of which type of device were not retained in clinic' (Sivin 1979). In the other the clients were blinded to the device (Sivin 1990).

The loss to follow-up rate was high in the Rosenberg trial. This trial also has the highest rates in both arms for the outcome that requires clinical involvement, namely removals for pain and/or bleeding. Women who wanted the device removed were required to attend a clinic, while those happy with the device may have defaulted. This may have biased the result but the direction of the bias is unknown. Removing the Rosenberg trial from the meta-analysis of discontinuations for pain and/or bleeding gives an identical result. Likewise, removing this trial has no appreciable impact on the meta-analyses of discontinuations for expulsions and pregnancies when the original inserter was used, as these meta-analyses are influenced mainly by the much larger and methodologically stronger WHO study.

AUTHORS' CONCLUSIONS

Implications for practice

There are insufficient data to show that the frameless IUD has overcome the problem of early expulsions. The skill of the clinician may continue to be the critical factor as regards early expulsions and pregnancies. This review does not support the use of GyneFix to reduce the risk of expulsion in general. Indeed, early reports from the UK suggest that expulsions may continue to be a problem with GyneFix, which do not appear to have been overcome. This however may not be the case where a clinician has a track record of successful insertions of GyneFix or where the position of the IUD can be confirmed with ultrasound scan. Early follow-up is important to identify unrecognised expulsions of the frameless device, and women should be encouraged to check for the presence of the IUD string.

The uncertainty about early expulsions is carried through to efficacy in preventing pregnancy, but even if clinicians experience the higher expulsions rates similar to that found with the earliest inserter used for the frameless device, the impact in terms of pregnancy will be small and may be compensated by superior efficacy later in use. Women can be advised that if GyneFix is not expelled within the first year, it is probably the most effective IUD available, although the absolute difference from other high-copper load IUDs is small and of doubtful clinical significance.

A new IUD that reduces the number of removals for bleeding and pain could have a clear advantage, as these are the main reasons for dissatisfaction and removal. Against expectations the frameless IUD has failed to achieve this. There appears to be no role for GyneFix in reducing excessive bleeding experienced with a standard IUD, and the evidence suggests that a woman with troublesome bleeding prior to insertion would be equally unsuitable to TCu380A and GyneFix. This may also apply to the less frequent situation of pain without excessive bleeding, although the data are less strong on this.

There are no randomised studies to support the use of GyneFix in situations where the anchoring technology may intuitively have an advantage, such as puerperal insertion or recurrent expulsions with a framed device.

It is unknown whether the evidence garnered in this review is relevant to nulliparous women as, apart from the brief DSouza trial, only women who had had children were included in the trials.

Implications for research

A large multicentre independent randomised trial of one years duration comparing the frameless device, using the new one-handed introducer, to TCu380A should satisfy the questions of failed insertions and, more importantly, of early expulsions. The study subjects and skills of the clinician should closely match the targeted population, with differing clinical settings and preferably

in non-specialist centres. The possibility of improved retention of the frameless device in situations with a greater risk of expulsion, such as immediately after childbirth and with a distorted uterine cavity, deserve attention in randomised studies.

The frameless device has not been studied beyond eight years of use, with limited data for the later two years. The large WHO trial provides a unique opportunity to provide evidence on long term use, hopefully up to 10 years and beyond.

The potential for reduced pain with the frameless device in nulliparous women warrants study.

Randomised bleeding studies using the GyneFix (Mini) may indicate whether reducing the copper load and size of the device has an impact on blood loss. If this is demonstrated a larger trial of this device is warranted.

Improved randomisation procedures are needed in IUD trials, especially in concealing the allocation sequence which is always possible, and more thought needs to be given to the possibilities of blinding the participants to the type of IUD used. For trials to

provide valid data, data should be analysed in groups to which participants are randomised. Allowing a proportion of participants to choose their preferred device after allocation (Dou 2001) severely undermines the reason for randomisation, the creating of similar treatment groups.

ACKNOWLEDGEMENTS

Patrick Rowe provided eight year data from the WHO trial. Dirk Wildemeersch, the developer of the frameless device, provided unpublished information on the Wu study, drew our attention to the Andrade study on menstrual blood loss and provided information on the development of the frameless device. Shangchun Wu provided data on the menstrual blood loss study. Rachel DSouza provided information on randomisation. Tim Farley (WHO) and Jan Vandenbroucke gave advice on the statistical methods used in this review, and Connie Smith offered helpful comments on the drafts. We would also like to thank the reviewers John Guillebaud, Lindsay Edouard, Ken Schulz and Patrick Rowe.

REFERENCES

References to studies included in this review

D'Souza 2003 *{published data only}*

D'Souza RE, Masters T, Bounds W, Guillebaud J. Randomised controlled trial assessing the acceptability of GyneFix versus Gyne-T380S for emergency contraception. *J Fam Plann Reprod Health Care* 2003;**29**(2):23–9.

Rosenberg 1996 *{published data only}*

* Rosenberg MJ, Foldes R, Mishell DR, Jr, Speroff L, Waugh MS, Burkman R. Performance of the TCU380A and Cu-Fix IUDs in an international randomized trial. *Contraception* 1996;**53**(4):197–203.

Rowe 1995 *{published and unpublished data}*

* Rowe PJ, Reinprayoon D, Koetsawang S, Shu-rong Z, Shang-chun W, Hui-min F, et al. The TCU 380A IUD and the frameless IUD 'the FlexiGard': Interim three-year data from an International Multicenter Trial. *Contraception* 1995;**52**(2):77–83.

Wu 2000 *{published and unpublished data}*

* Wu S, Hu J, Wildemeersch D. Performance of the frameless GyneFix and the TCU380A IUDs in a 3-year multicenter, randomized, comparative trial in parous women. *Contraception* 2000;**61**(2):91–8. [MEDLINE: 20263661]

Wu S, Hu J, Wu M. Randomized comparative study of GyneFix IN and TCU 380A intrauterine devices. *Chung Hua Fu Chan Ko Tsa Chih* 1998;**33**(6):345–8. [MEDLINE: 20266635]

References to studies excluded from this review

Cao 2000 *{published data only}*

Cao X, Zhang W, Gao G, Van Kets H, Wildemeersch D. Randomized comparative trial in parous women of the frameless

GyneFix and the TCU380A intrauterine devices: long-term experience in a Chinese family planning clinic. *Eur J Contracept Reprod Health Care* 2000;**5**(2):135–40.

Dou 2001 *{published data only}*

Dou JL, Zhang Y, Zhang CY, Xin XF, Wang JY. Clinical comparative study of GyneFix IN and ML Cu375 intrauterine devices. *Reproduction and Contraception* 2001;**12**(3):181–5.

Hui-Qin 1999 *{published data only}*

Hui-Qin L, Zhuan-Chong F, Yu-Bao W, Yiao-Lin H, Van Kets H, Wildemeersch D. Performance of the frameless IUD (Flexigard prototype inserter) and the TCU380A after six years as part of a WHO multicenter randomized comparative clinical trial in parous women. *Adv Contracept* 1999;**15**(3):201–9.

Additional references

Andersson 1998

Andersson K, Ryde-Blomqvist E, Lindell K, Odland V, Milsom I. Perforations with intrauterine devices. Report from a Swedish survey. *Contraception* 1998;**57**(4):251–5. [MEDLINE: 98313603]

Andrade 1993

Andrade AT, Araujo DA, Abranches AA. Comparative study of intrauterine devices: TCU380A and Flexigard. *Boletim Do Centro De Biologia Da Reproducao*. 1993;**12**(1):16–9..

Aust 2003

Aust TR, Kirwan JN, Herod JJ, McVicker JT. Perforation with the GyneFix intrauterine implant: is there a common factor?. *J Fam Plann Reprod Health Care* 2003;**29**(3):155–6.

Batar 1992

Batar I. One-year clinical experience with FlexiGard. *Contraception* 1992;**46**(4):307–12.

Brockmeyer 2004

Brockmeyer A, Kishen M, Webb A. New GyneFix introducer. *J Fam Plann Reprod Health Care* 2004;**30**(1):65.

Cao 2004

Cao X, Zhang W, Zhao X, Lin N, Wang L, Li C, Song L, Zhang Z, Wildemeersch D. Three-year efficacy and acceptability of the GyneFix 200 intrauterine system. *Contraception* 2004;**69**(3): 207–11.

Deeks 2004

Deeks JJ, Higgins J, Altman DG. Analysing and presenting results. In: Alderson P, Green S, J H editor(s). *Cochrane Reviewers Handbook 4.2.2 [updated March 2004]*. Vol. **Section 8**. <http://www.cochrane.org/resources/handbook/hbook.htm> (accessed 31st January 2004)., Cochrane Collaboration, 2004.

Dennis 2001

Dennis J, Webb A, Kishen M. Expulsions following 1000 GyneFix insertions. *J Fam Plann Reprod Health Care* 2001;**27**(3):135–8.

Eskandar 2003

Eskandar OS, Eckford SD. Intravesical migration of a GyneFix intrauterine device. *J Fam Plann Reprod Health Care* 2003;**29**(4): 237–8.

Farley 1986

Farley TM. Life-table methods for contraceptive research. *Stat Med* 1986;**5**(5):475–89. [MEDLINE: 87069193]

Farley 2001

Farley TM, Ali MM, Slaymaker E. Competing approaches to analysis of failure times with competing risks. *Stat Med* 2001;**20** (23):3601–10.

Faundes 2000

Faundes D, Perdigo A, Faundes A, Bahamondes L, Petta CA. T-shaped IUDs accommodate in their position during the first 3 months after insertion. *Contraception* 2000;**62**(4):165–8.

Geyoushi 2002

Geyoushi BE, Randall S, Stones RW. GyneFix: a UK experience. *Eur J Contracept Reprod Health Care* 2002;**7**(1):7–14.

Harrison 1996

Harrison PF, Rosenfield A. *Contraceptive research and development: looking to the future*. Washington, D.C.: National Academy Press, 1996. [: 0309054427]

Hasselblad 1995

Hasselblad V, McCrory DC. Meta-analytic tools for medical decision making: a practical guide. *Med Decis Making* 1995;**15**(1): 81–96.

Hawkins 1979

Hawkins DF, Elder MG. *Human fertility control: theory and practice*. London: Butterworths, 1979. [: 0407001271]

Kleinbaum 1982

Kleinbaum DG, Kupper LL, Morgenstern H. *Epidemiologic research: principles and quantitative methods*. Belmont, Calif.: Lifetime Learning Publications, 1982:xix, 529. [: 0534979505]

Masters 2000

Masters T. Review of first two hundred women to be fitted with GyneFix at Margaret Pyke Centre (Abstract). Annual Symposium Faculty of Family Planning and Reproductive Health Care. London: Faculty of Family Planning and Reproductive Health Care, 2000:13.

O'Brien 2004a

O'Brien P. A comparison of Pearl indices and cumulative incidences for use in meta-analysis of contraception trials. *European Journal of Contraception and Reproductive Health Care* 2004;**9**(Supplement 1): 32.

O'Brien 2004b

O'Brien P. The TCu380 Slimline or TCu380A: a systematic review of comparative data. *European Journal of Contraception and Reproductive Health Care* 2004;**9**(Supplement 1):93.

O'Brien 2004c

O'Brien P. The effects of increasing the copper load on IUD performance: a systematic review. *European Journal of Contraception and Reproductive Health Care* 2004;**9**(Supplement 1):93.

Reuter 2001

Reuter S, Krishnamurthy S. Intra-uterine implant (GyneFix) lost via intestinal route?. *J Fam Plann Reprod Health Care* 2001;**27**(3): 159–60.

Schulz 1995

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *Jama* 1995;**273** (5):408–12..

Sivin 1979

Sivin I, Stern J. Long-acting, more effective copper T IUDs: a summary of U.S. experience, 1970-75. *Studies in Family Planning* 1979;**10**(10):263–81.

Sivin 1990

Sivin I, Shaaban M, Odland V, Olsson SE, Diaz S, Pavez M, et al. A randomized trial of the Gyne T 380 and Gyne T 380 Slimline Intrauterine Copper devices. *Contraception* 1990;**42**(4):379–89.

Sivin 2004

Sivin I. Failing in analysis of the performance of the gynefix 200 intrauterine system. *Contraception* 2004;**70**(4):353–4; author reply 354–5.

Tai 2001

Tai BC, Peregoudov A, Machin D. A competing risk approach to the analysis of trials of alternative intra-uterine devices (IUDs) for fertility regulation. *Stat Med* 2001;**20**(23):3589–600.

Tatum 1989

Tatum HJ, Connell EB. Intrauterine contraceptive devices. In: Filshie M, Guillebaud J editor(s). *Contraception: science and practice*. London: Butterworths, 1989. [: 0407017208]

Tietze 1973

Tietze C, Lewit S. Recommended procedures for the statistical evaluation of intrauterine contraception. *Studies in Family Planning* 1973;**4**(2):35–42.

Treiman 1995

Treiman K, Liskin L, Kols A, Rinehart W. IUDs - an update. *Popul Rep B* 1995;**6**:1–35. [MEDLINE: 96315838]

Van Kets 1997

Van Kets H, Van der Pas H, Thiery M, Wildemeersch D, Vrijens M, Van Trappen Y, et al. The GyneFix implant systems for interval, postabortal and postpartum contraception: a significant advance in long-term reversible contraception. International Study Group on Intrauterine Drug Delivery. *Eur J Contracept Reprod Health Care* 1997;**2**(1):1–13. [MEDLINE: 98343075]

Vekemans 1999

Vekemans M, Verougstraete A. Late uterine perforation with an anchored IUD, the Gynefix: a case report. *Contraception* 1999;**60**(1):55–6. [MEDLINE: 20017220]

Wildemeersch 1988

Wildemeersch D, Van Der Pas H, Thiery M, Van Kets H, Parewijck W, Delbarge W. The Copper-fix (Cu-Fix): A new concept in IUD technology. *Adv Contraception* 1988;**4**(3):197–205.

Wildemeersch 1999

Wildemeersch D, Batar I, Webb A, Gbolade BA, Delbarge W, Temmerman M, et al. GyneFIX. The frameless intrauterine contraceptive implant--an update for interval, emergency and postabortal contraception. *Br J Fam Plann* 1999;**24**(4):149–59. [MEDLINE: 99153941]

Wildemeersch 2004

Wildemeersch D. GyneFix insertion. *J Fam Plann Reprod Health Care* 2004;**30**(2):131.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

D'Souza 2003

Methods	<p>Individual randomisation in blocks of 10. Random sampling table used for allocating sequence, allocation concealment by sealed envelope. Inserting doctor not blinded. Patients blinded. Assessment at follow-up was blinded in 88%.</p> <p>Power calculation reported.</p> <p>Single specialist centre, London.</p> <p>Two arm design. Group A, IUD for emergency use only. Poor recruitment to this arm, not included in analysis. Group B for planned long-term use. Group A arm discontinued because of poor recruitment. Results relate to intended long-term use arm only. Data not provided on Group A.</p> <p>Duration of study: 6 weeks.</p> <p>Exclusions from analysis: one failed GyneFix insertion.</p> <p>Statistical methods used: difference in mean for continuous variables, p values only for dichotomous outcomes.</p> <p>Partly funded by manufacturer of GyneFix.</p> <p>No mention of consumer involvement.</p> <p>Dec 1998 to Dec 2000</p>
Participants	<p>192 women</p> <p>Group A: 10 GyneFix, 7 NovaT</p> <p>Group B: 90 GyneFix, 85 TCu380S</p> <p>Inclusion criteria: women requiring emergency IUD.</p> <p>Exclusion criteria: suspected pregnancy, lactation, current pelvic infection, immunosuppressive therapy, history of bacterial endocarditis, valvular heart disease, any prosthesis which could be prejudiced by blood-borne infection, Wilson's disease, previous IUD insertion during current menstrual cycle, uterine cavity markedly distorted, uterine cavity length less than 5.5 cm.</p> <p>All participant had pregnancy test and screening for chlamydia trachomatis at IUD insertion and were offered prophylactic antibiotics.</p>
Interventions	<p>Group A (short-term use only): GyneFix or Nova-T 200</p> <p>Group B (planned long-term use): GyneFix or TCu380S</p> <p>All inserting doctors were experienced with both devices.</p> <p>All women were encouraged to accept oral mefenamic acid 500 mg prior to IUD insertion, and para-cervical local anaesthetic was offered</p>
Outcomes	<p>Pain of insertion (primary outcome), assessed at insertion and at 6 weeks using visual analogue scale, verbal description, doctors assessment. Duration of pain on insertions day.</p> <p>Number experiencing pain in 30 days subsequent to day of fitting, recorded in diary.</p> <p>Bleeding: number of bleeding episodes, number of days spotting or bleeding, in subsequent 30 days after insertion, recorded in diary. Definitions: 'bleeding' - requiring sanitary protection, 'spotting' - light or no sanitary protection.</p> <p>Failed insertions.</p> <p>Expulsions at 6 weeks.</p> <p>Perforations at 6 weeks.</p> <p>Pelvic inflammatory disease (diagnostic criteria given) at 6 weeks.</p> <p>Pregnancies at 6 weeks.</p>

D'Souza 2003 (Continued)

Notes	TCu380S similar to TCu380A, except that the copper sleeves are flush with, and placed at the ends of, the arms. Follow-up 98%, by post for 4 and telephone for 3. Assessment at follow-up occurred at more than 7 weeks in 20%.	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Rosenberg 1996

Methods	Individual randomisation in blocks of 4. Computer generated allocation sequence. Allocation concealment described as 'At enrolment each subject was entered into a computer database which the investigator could not access'. Blinding of participants not reported. Evidence of power calculation. Conducted in 22 sites in US and Europe. Recruited Aug 1989-December 1992. 115 excluded in analysis (date or type of IUD inserted not recorded (22), inserted after enrolment closed (6), 6 centres (87 women) were excluded because of non-compliance with protocol ['inadequate access for study monitoring, 40% or more subjects had no recorded reason for termination, or if <10 subjects involved']. Of these 87, 76% did not have reason for termination recorded). Tietze and Lewit methods used for gross rates (single decrement), standard error according to Potter. Cut-off date not given. Funding from GynoPharma Inc - manufacturer of T380A. No consumer involvement described.	
Participants	Inclusion criteria: healthy, parous women, sexually active, 18-40 years, more than 3 months post-partum or post second trimester abortion or one month post first trimester abortion and at least one menstrual period or withdrawal bleeding episode. Exclusion criteria: clinical evidence of pregnancy or history of ectopic pregnancy, pelvic inflammatory disease, infection with Neisseria gonorrhoea or Chlamydia trachomatis, evidence of jaundice, diabetes, anaemia or pregnancy. 989 women randomised. Included in analysis: 427 with TCu380A and 447 with Cu-Fix. Insertion failures not reported. Mean age 31.2 for TCu380A and 30.9 for frameless IUD. Mean parity of 2.0 for TCu380A and 1.9 for frameless IUD. No data given on menstrual cycle, presence of uterine fibroids or previous contraception usage.	
Interventions	TCu380A or Cu-Fix frameless IUD. Insertions techniques not described. No training for inserters described.	
Outcomes	Cumulative discontinuation rates at one and two years for: pregnancy rates, expulsions,	

Rosenberg 1996 (Continued)

	<p>removal rates for pain and/or bleeding, other medical terminations, pelvic inflammatory disease, non-medical removals. loss to follow-up Continuation rate. Number of women completing interval. Women-months of experience. The diagnosis of pregnancy was made clinically. Assessed at scheduled visits at 1, 6, 12, and 24 months.</p>
--	---

Notes	<p>Loss to follow-up rates overall were 18.% for TCU380A and 15.7% for Cu-Fix. Cumulative loss-to-follow-up rate (SE) at one year for TCU380A was 9.9 (1.6), and 13.0 (1.8) for Cu-Fix. The corresponding rates at two years were 23.7 (3.1) and 26.7 (3.2). The differences were not significant.</p>
-------	--

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Rowe 1995

Methods	<p>Individual randomisation in blocks of 10. Computer list used for allocation sequence, allocation concealment by sealed envelope. Inserters not blinded, no data on blinding of other participants. No evidence of power calculation. Conducted in 13 developing and transitional countries. 28 centres, 6 of which did not participate in the main phase because of poor results (1), failure to adhere to protocol (5). Insertions: pilot phase 1988-91 (28 centres, 40 insertion each), 26% of all insertions; main phase initiated 1991-92, ongoing. Only exclusions described were for failed insertions - one women randomised to TCU 380A and 53 randomised to frameless IUD. Statistical methods for cumulative rates: daily life-table method (single decrement). Cut-off 31/12/99. Institutional funding. No consumer involvement.</p>
---------	---

Participants	<p>Inclusion criteria: healthy, parous, informed women with no contraindications to IUD use. Exclusions criteria: history of PID or pelvic abscess since last pregnancy, < 6 weeks since parturition or abortion, history of ectopic pregnancy, recent sexually transmitted infection, undiagnosed genital tract bleeding, congenital genital tract malformation, known or suspected genital tract malignancy, multiple uterine fibroids with menstrual disorders, clinical or laboratory evidence of anaemia, history of hydatidiform mole in last pregnancy. Number randomised not given. Number of insertions 2185 TCU380A, one failed insertion; 2155 frameless IUDs with 53 failed insertions. Mean age (sd) 29.8 (4.7) for TCU380A and 29.9 (4.0) for frameless IUD. No difference in parity between groups.</p>
--------------	---

Rowe 1995 (Continued)

	No data given on whether recent pregnancy, menstrual cycle, sexual activity or previous contraception usage.	
Interventions	TCu380A or FlexiGard frameless IUD. Insertions techniques was described. No training for TCu380A, training workshop for all investigators in insertions technique for frameless IUD.	
Outcomes	Cumulative net discontinuation rates and standard error in percent for total pregnancy intrauterine pregnancy ectopic expulsions total medical removals total pain and/or bleeding pain bleeding pain and bleeding pelvic inflammatory disease other medical removals loss to follow-up continuation rate. Number of women completing interval. Women-years of experience. Method of diagnosis of pregnancy not specified. Assessment at 3, 6, 12 months, then yearly.	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Wu 2000

Methods	<p>Individual randomisation in blocks of 10. Computer generated allocation sequence, sealed envelopes for concealment. Inserters not blinded, no other information on masking. Power calculation done but not reported. 6 centres in China, 3 years (ongoing). Insertions July 94-Nov 95. Daily life-table methods to calculate discontinuation rates, single decrement model. Cut-off date 3 years + 30 after insertion, analysis 18/6/99. Funding from Control Europe nv/sa (manufacturers or GyneFix). No consumer involvement.</p>
Participants	<p>Inclusion criteria: not given. Exclusions: nulliparity, history of PID or pelvic abscess since last pregnancy, < 6 weeks since parturition or abortion, history of ectopic pregnancy, recent sexually transmitted infection, undiagnosed genital tract bleeding, congenital genital tract malformation, known or suspected genital tract malignancy, multiple uterine fibroids with menstrual disorders, clinical or laboratory evidence of anaemia, history of hydatidiform mole in last pregnancy. Number randomised not given, 305 attempted insertion of TCu380A (no failures), 301 attempted insertions of GyneFix with one failed insertion. Mean age 29.8 for TCu380A and 30.4 for frameless IUD. Mean parity of 1.0 for TCu380A and 1.0 for GyneFix. No data given on recent pregnancy, menstrual cycle, sexual activity or previous contraception usage.</p>
Interventions	<p>TCu380A or GyneFix frameless IUD. Insertions techniques was described. No special training courses as 'the investigators had already some experience with the anchoring technique' used with the frameless device.</p>
Outcomes	<p>Scheduled visits at (1), 3, 6, 12 months and then yearly, and any time if problem or on request. Definition of outcomes as defined by Tietze. Events and cumulative net discontinuation rates and standard error in percent at 1, 2 and 3 years for total pregnancy expulsions perforations total medical removals total pain and/or bleeding pain bleeding pain and bleeding pelvic inflammatory disease other medical removals total use-related loss to follow-up continuation rate. Number of women completing interval. Women-years of experience. Method of diagnosis of pregnancy not specified. Assessed at scheduled visits after first menstruation, at 3, 6, 12 months and then yearly.</p>
Notes	

Wu 2000 (Continued)

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Characteristics of excluded studies *[ordered by study ID]*

Cao 2000	This trial was conducted in two phases, 1990/91 (199 insertions) and 1995 (114 insertions). FlexiGard was used in the early period and GyneFix later. This trial was excluded as the data from the early phase is already included in the WHO trial (Tianjin centre) (Rowe 1995)
Dou 2001	Excluded because a proportion of the participant were not randomised. If participants did not want the device allocated they were allowed to choose the alternative and were included in the analysis (Dou personal communication)
Hui-Qin 1999	This report describes the six-year experience in one centre, Shanghai, of the WHO multicentre trial and is included in the six-year data for the latter (Rowe 1995).

DATA AND ANALYSES

This review has no analyses.

WHAT'S NEW

Last assessed as up-to-date: 12 November 2004.

15 April 2008	Amended	Converted to new review format.
---------------	---------	---------------------------------

HISTORY

Protocol first published: Issue 3, 1999

Review first published: Issue 3, 2001

13 November 2004	New citation required and conclusions have changed	Substantive amendment
------------------	--	-----------------------

CONTRIBUTIONS OF AUTHORS

Paul O'Brien conceived the idea, drafted the protocol, searched the literature, performed the data extraction, assessed the quality of studies, performed the statistical analysis and drafted the report. Caroline Marfleet commented on draft protocol, performed the data extraction, checked the statistical analysis, and contributed to the final report.

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- Westminster PCT, London, UK.

External sources

- No sources of support supplied

I N D E X T E R M S

Medical Subject Headings (MeSH)

*Contraception; *Intrauterine Devices [adverse effects]; Equipment Design; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans