REVIEW

New technologies in contraception

Running title: New technologies in contraception

S Rowlands

Warwick Medical School

Correspondence to: Dr Sam Rowlands, Masters Accredited Programmes Directorate, Warwick Medical School, Gibbet Hill Campus, University of Warwick, Coventry CV4 7AL, UK

Tel: 07738 269852

E-mail: sam.rowlands@warwick.ac.uk

Abstract

New technologies in both reversible contraception and sterilisation are described. The review includes recent advances in the development of oral contraception, emergency contraception, injectables, vaginal rings, subdermal implants, transdermal contraception, intrauterine devices, spermicides and barrier methods. It also covers methods of transcervical female sterilisation and more easily reversible male sterilisation. The emphasis is on the technology and its safety and effectiveness. Hormonal delivery systems are described in some detail. Mention is also made of research into vaccines and male hormonal methods, where progress has been disappointing.

Context

Technology is of limited value unless governments can supply their populations with contraceptive services and supplies. In many developing countries, individuals and couples who cannot afford to purchase contraceptives do not enjoy the human right to decide on the number and spacing of their children. More than 200 million women in the developing world are not using any form of contraception or using traditional methods only[1]. Governments and individuals should work towards the Millennium Development Goal target of universal access to reproductive health services by 2015 through the primary care health system.

Uptake of contraception is variable around the world, varying from 3% in Chad to 90% in China in women aged 15 – 49 who are married or in a union[2]. Uptake is high in the UK, but methods used are still predominantly pill and condom[3]. Despite the

advent of long-acting reversible contraceptive (LARC) methods[4], these remain minority methods: for example implants were used by only 1% of women aged 16 – 49 in Britain in 2006[3]. Use of any method of contraception, regardless of its degree of effectiveness, is better than using no method. But there are large differences in effectiveness between the methods: for instance a 300-fold difference between typical use failure rates of male condom and subdermal implant[5]. Simultaneous use of methods where one is a barrier method dramatically lowers the risk of unintended pregnancy as well as giving sexually transmitted infection (STI) protection, known as dual protection. Most women and men still perceive contraceptive choice as a matter of finding the 'least worst' option, balancing effectiveness and ease of use against perceptions and expectations of adverse effects and health risks[6].

Many men are willing to take on the side effects and health risks of contraceptive use[7]. A cross cultural survey found that women felt the contraceptive burden too frequently falls to them and they welcomed the availability of a reversible male contraceptive which they would trust their partners to take[8].

Oral contraception

Newer progestogens[9;10] have been used in combined pills: dienogest, nomegestrol and drosperinone. All three progestogens have antiandrogenic activity; drospirenone has antimineralocorticoid activity. Newer progestogens are being produced in order to develop novel positive attributes, enhance positive attributes of existing progestogens or to reduce or eliminate undesirable attributes.

Dosage of both oestrogen and progestogen has been markedly reduced in recent years. Hitherto, ethinylestradiol (EE) has been the main oestrogen used in combined

pills. Further work is being done on the use of estradiol (E_2) in the combined pill; previous attempts had been thwarted by poor cycle control. The rationale for this is that a natural steroid would be expected to be less thrombogenic than synthetic oestrogens[11] and less likely to increase breast cancer risk. An E_2 / drospirenone combination is being studied in both monophasic and triphasic formulations in Germany with respect to cycle control and safety. E_2 has been combined with dienogest in a quadriphasic formulation. This product has been shown to provide efficient ovulation inhibition[12]. When compared with a 20mcg levonorgestrel (LNG) pill in a randomised controlled trial (RCT), cycle control and side effect profile was as good as the LNG pill[13]. E_2 has also been combined with nomegestrol; a trial in the Netherlands investigating ovarian function which compares E_2 / nomegestrol with EE / drospirenone has been completed. Recently, estetrol (E_4) a steroid produced by the human fetal liver has been studied. E_4 is about 18 times less potent than EE, so fewer adverse effects would be predicted. Preliminary work on combinations with progesterone or desogestrel has been undertaken[14]. There is a possibility that E_4 might be protective against breast cancer; it is classified as a natural selective oestrogen receptor modulator.

Other types of work on combined pills have perhaps been less original but nevertheless have the potential for considerable impact on women's lives. Extended use of the combined pill has become widespread; running several or all packets together reduces bleeding days and menstrual cycle-related symptoms[15]. When used continuously for one year, 18% of women achieve amenorrhoea by three months of use and 88% by 10 months[16]. Bleeding is significantly decreased in continuous users compared to cyclical users, with an average of three days in cycles 1 to 3 (vs 10 days, $p<.001$) and 0 days for cycles 10 to 12 (vs. 9 days, $p<.001$).

Formulations of 30 mcg of EE and 150mcg of LNG with 84 pills per packet have become available, giving a 91-day cycle[17]. Sixty per cent of women using a monophasic formulation containing EE 20mcg and LNG 90mcg with 28 pills in a packet, reported amenorrhoea within one year[18]. It has also been shown that shortening the pill-free interval below seven days results in more effective ovarian suppression[19]: combined pills have become available with 24 pills per packet[20;21].

Mifepristone is a selective progesterone receptor modulator (PRM) or antiprogestogen. PRMs block receptors in the ovary, inhibit the luteinising hormone surge and have a powerful endometrial effect. Mifepristone has been studied in a phase-2 trial at a daily dose of 5mg compared to an LNG progestogen-only pill[22]. It was shown to be an effective pill with a better bleeding pattern than the progestogen-only pill. More women were amenorrhoeic while taking mifepristone than progestogen-only pill (49 vs 0% p<.001) and fewer women bled or spotted for more than five days per month (4 vs 39% p<.001). There were no pregnancies in 356 months of exposure in women who used only mifepristone for contraception. In a Chinese pilot study, once weekly mifepristone at a dose of 25mg showed potential as an oral contraceptive pill[23]. Among 76 women, no pregnancies occurred in 456 cycles. During the six study cycles, there was a persistent trend toward fewer bleeding days and more amenorrhoea.

Another PRM, VA2914, has been piloted as a daily pill[24]. Forty-six women took this for 84 days and ovulation was suppressed in 80% of women without inducing hypo-oestrogenism.

The development of oestrogen-free oral contraception has significant advantages in relation to acceptability and safety. Many women prefer to have either predictable bleeding less often than once a month or not to bleed at all[25;26]. Amenorrhoea during

mifepristone use is not accompanied by hypo-oestrogenism and there are theoretical reasons for thinking that breast cancer risk may be reduced.

Emergency contraception

The combined oestrogen-progestogen regimen was superseded by the progestogen-only method. The latter has now been combined into one dose. Mifepristone has been used in trials for emergency contraception since the early 1990s. Mifepristone has just as good efficacy as emergency contraception at a dose of 10mg as at a dose of 600mg[27]. Mifepristone has effectiveness equivalent to LNG 1500mcg when used as hormonal emergency contraception[28]. At present no pharmaceutical company wants to pursue marketing for this purpose because of the political connotations of its abortifacient effect. In addition, further toxicology testing would be needed in order to obtain a licence for use as long-term contraception.

Another PRM, CDB-2914, not known to have abortifacient properties has been shown in an RCT to have comparable efficacy to LNG[29]. Although PRMs have endometrial inhibitory activity, this is probably not a significant mechanism of action at the low doses used for emergency contraception[30]. Thus, all methods of emergency contraception investigated so far have as their main mechanism of action either blockade or delay of ovulation. This raises the point that effectiveness of currently available hormonal emergency contraception may be inferior in the luteal phase; there is a suggestion that this is so for LNG[31].

It has also been shown that meloxicam, a cox-2 inhibitor, can prevent rupture of the dominant follicle even after the ovulatory process has been triggered by the luteinising hormone surge and so its addition to LNG might improve the efficacy of

LNG emergency contraception[32]. A similar delay in follicular rupture has been found using rofecoxib[33].

Injectable contraception

Depot medroxyprogesterone acetate (DMPA) has been licensed for long term use in the UK since 1982. Stimulated by reports of a possible negative effect on bone health[34], micronised subcutaneous medroxyprogesterone acetate 104mg/ 0.65mL has been produced, which is a 30% dose reduction compared to the standard formulation. This formulation has a slower rate of absorption and lower peak serum levels than intramuscular DMPA and is given at the same interval. Two large phase-3 non-comparative trials of subcutaneous DMPA have shown high effectiveness and a good tolerability profile. Amenorrhoea rates of 55% at 12 months were found with subcutaneous DMPA, compared to about 50% with the intramuscular formulation[35]. There have been no published studies so far of subjects using self-injection of subcutaneous DMPA[36].

Two combined products, both given monthly, have been developed by the World Health Organization (WHO). These injectables are now available in many countries after extensive trials in South America and China from the 1960s onwards. They both add E_2 to existing injectable progestogens. The first product is medroxyprogesterone acetate 25mg with estradiol cypionate 5mg and the second is norethisterone enanthate 50mg with estradiol valerate. Compared to progestogen-only injectables, combined injectables disturb bleeding patterns less[37] and allow earlier return to ovulation after discontinuation[38]. Bleeding patterns are similar to the combined pill, patch or ring. Effectiveness has been shown to be good in studies of everyday use[39]. Pilot studies show that self-injection of monthly injectables is feasible[40].

Vaginal rings

Delivery of sex steroids via the vaginal route offers several advantages: steroid absorption through the vaginal epithelium is rapid, technology allows a constant release rate, the method is under the woman's control and she can remove the ring for sex for up to 2 hours. Problems associated with first-pass metabolism and with reduced hormone absorption due to gastrointestinal problems are avoided. The use of safe and pliable polydimethylsiloxane carriers and the development of hormone-containing controlled-release polymers have permitted the manufacture of rings that can release hormone for up to one year[41]. All vaginal rings come within the definition of long-acting reversible contraceptives, that is administration once per cycle or less often[4]. Acceptability is high among self-selected women taking part in trials, with many women changing their minds about which method of contraception they perceive to be best, from the combined pill to the combined ring, after a few cycles of use[42].

The first combined ring to be widely introduced releases 120mcg etonogestrel and 15mcg EE / day from an ethylene vinyl acetate (EVA) copolymer ring. Women use a ring for three weeks followed by a ring-free week during which time they have a withdrawal bleed. A new ring is needed for each four-week cycle. Steady state hormone release is achieved within three days of insertion. Continuous serum hormone levels are achieved with ring use, avoiding the peaks and troughs seen with the combined pill. Systemic exposure to EE has been shown to be lower for the combined etonogestrel ring than for both the transdermal patch and a 30mcg pill[43]. Two comparative trials showed high efficacy no different from the combined pill, especially when adherence is good[44;45]. Evidence from both clinical studies and clinical experience programmes shows better cycle control than with the combined pill[46-49]. The ring can however cause leucorrhoea, vaginal discomfort, vaginitis and

ring-related events comprising foreign body sensation, coital problems and expulsion[44;45].

Nestorone rings have undergone preliminary investigation by the Population Council[41]. Nestorone (formerly known as ST-1435) is ineffective orally, but due to its high progestogenic potency when given systemically, low doses are sufficient for contraceptive efficacy. Rings releasing a combination of nestorone[9;10] at a dose of 150 or 200mcg / day with EE 15 or 20mcg / day are effective for 12 months and so are more cost effective. Phase-3 trials are ongoing.

Progestogen-only vaginal rings are less effective than combined rings but have a particular application in lactating women as they are oestrogen-free. A ring releasing progesterone 10mg / day can be used for up to four months; it is on the market in Chile and Peru[50]. Rings using nestorone are particularly apposite due to rapid inactivation when taken orally and so the suckling baby cannot possibly be affected[9]. Nestorone-releasing rings are effective for up to one year[51].

In view of the powerful antiovulatory effect of nestorone, twice that of LNG, a phase-1 study was conducted into the potential of the nestorone combined ring for use as emergency contraception in women not at risk of pregnancy[52]. Judging by ultrasound scanning and hormonal profiles, the ring appears to be more effective in disrupting ovulation when given in the follicular phase and ovulation was absent after the ring had been in situ for seven days. Like the copper intrauterine device (IUD), this method could be used as ongoing contraception too.

The Population Council has started investigating the possibility of using the PRM, CDB-2914, in a vaginal ring.

Subdermal implants

Implant technology has been improved considerably. Pharmacokinetics approaching zero-order release is now possible; this means that the release is constant over time and serum levels are steady. The original LNG implant had the disadvantage of comprising six capsules which made insertion and removal lengthy and sometimes difficult and so local complications more likely. The capsules were hollow polymer tubes filled with free steroid crystals and quite easily torn or divided by forceps or scalpel. Newer systems consist of either one or two implants and these are now usually solid rods filled with a mixture of steroid crystals and polymer which are much more robust, but still flexible.

Contraceptive implants are highly effective[4], higher even than vasectomy[5]. Bleeding disturbances remain the single most problematic side effect of implants and the newer implants are no different in this respect.

LNG implants are now available in the form of two silastic rods releasing around 50mcg / day per rod and lasting for five years[53]. Single-rod etonogestrel (3-keto desogestrel) in EVA polymer implants give an initial release rate of about 60mcg / day which maintains serum levels well above those needed to inhibit ovulation (90pg/mL) for three years[54]. They are inserted using a disposable applicator. A trial is in progress to evaluate a modified etonogestrel implant applicator together with a radio-opaque rod; the latter would assist in the event of a difficult removal.

A nestorone implant in the form of a single rod releases steroid from a silicone matrix core and has completed phase-2 trials. This implant provides effective contraception

for two years and has higher acceptance by lactating women who have a more favourable bleeding pattern than by those women who do not breast feed[55].

Nomegestrol acetate[9;10] has been developed in Monaco. It is a potent progestogen, exerting a strong effect on the endometrium. Release of about 1000mcg / day from a one-year single silastic rod inhibits ovulation effectively[56]. A multicentre trial in more than 1500 women showed a low pregnancy rate and a discontinuation rate of only 16% at one year. However, there is no plan to commercialise this product.

Biodegradable implants have the advantage of not needing removal, so that the possibility of difficult removals is eliminated. LNG has been studied in a phase-2 trial as a single capsule composed of the polymer caprolactone over a period of one year[57]. The release of LNG from caprolactone is ten times faster than from the silastic in the original implant, allowing a big decrease in size of implant. Norethisterone 85% with cholesterol 15% mixed by a heat fusion technique has been studied in the form of four or five pellet systems[58].

Transdermal administration

With the successful development of matrix technology it has been possible to deliver both EE and progestogens through the skin. Norgestimate and its active metabolite norelgestromin can be delivered through a transdermal patch, remaining active for seven days. A combined patch which releases EE 20mcg / day and norelgestromin 150mcg / day is now widely available. The patch comprises three layers: an outer protective layer of polyester, a medicated adhesive middle layer and a clear polyester release liner which is removed just before application. Adherence to the regimen of use is better with the patch than with the combined pill, especially in teenagers[59].

Systemic exposure to EE is higher with the patch than with a 30mcg pill, despite the fact that it releases less EE than the pill[43]. Effectiveness is as good as the combined pill overall, but not in those who weigh more than 90kg[60]. Breakthrough bleeding and mastalgia are more common in cycles 1 and 2 with the patch than with the combined pill but thereafter there is no difference[59]. Three per cent of subjects discontinue the patch due to skin reactions[59].

Another patch is being developed: this patch releases 50mcg / day of gestodene and 18mcg of EE and was shown to suppress ovulation in all 199 subjects in a study over two cycles[61].

Nestorone has also undergone preliminary evaluation in the form of both a gel[62] and a spray[63] . In trials with the gel, mean serum levels of 150pmol/L were observed, achieving 83% ovulation suppresssion. The Metered Dose Transdermal System® (Acrux Ltd, Melbourne, Australia) is a precisely engineered spray that is capable of delivering drugs to the skin surface from they can be rapidly absorbed into the stratum corneum which acts as a drug reservoir. Steady state levels of nestorone were shown to be achievable with a single daily application of this spray. The mean

serum level was 391 pmol/L after five days. This is above the level of 250 pmol/L needed to suppress ovulation in at least 98% of subjects.

Intrauterine devices

Extensive experience from trials and evidence from systematic reviews has shown the TCu380S IUD and the LNG intrauterine system (IUS) to be the most effective intrauterine devices developed so far[64]. As the TCu380S and TCu380A can remain in place for up to ten years, their cost effectiveness is particularly high[64]. Sivin has suggested that such devices can retain their efficacy for up to 20 years[65]. A frameless device, the GyneFix® (Contrel, Ghent, Belgium), has been found to have comparable effectiveness to the TCu380A[66], but the effectiveness of the frameless device may be compromised by a higher rate of expulsion. Effectiveness of copper IUDs is almost as good as female sterilisation and of the IUS better than female sterilisation[5].

The development of frameless intrauterine devices has been pursued because plastic frames increase blood loss and pain. These devices have a very different insertion mechanism which requires specific training and achievement of a high level of operator skill; performance of frameless devices inserted by those with less experience is not so good. GyneFix® consists of six copper sleeves threaded on a length of polypropylene suture material. A knot at the proximal end is placed in the fundal myometrium, so anchoring the device. Long term efficacy has been demonstrated in a randomised comparative WHO trial[67].

The LNG-IUS is a now well-established method that for some time has been the only device of its type. Other designs have now been developed. Femilis™ (Contrel, Ghent, Belgium) has shorter side arms than the original LNG-IUS. Initial studies

show good clinical performance[68]. Insertion is by a simple push-in technique, as with a Multiload, and the device is well accepted by nulliparae. There are no comparative effectiveness studies. FibroPlant® (Contrel, Ghent, Belgium) is a frameless intrauterine system with a LNG-releasing EVA delivery system[69]. Two versions are being developed, releasing 14 and 20mcg LNG / day respectively. These IUSs have a lifespan of five years. A metal clip is placed 1 cm from the anchoring knot which locates the device on ultrasound or X-ray. FibroPlant® is suitable for insertion into uteri of any shape or size[70]. There are as yet no published data on the contraceptive efficacy of this device.

The Population Council has started to investigate the possibility of using the PRM, CDB-2914, in an IUS.

Spermicides

In view of the increase in incidence of STIs and HIV, much effort has been put into the development of spermicides that have additional microbicidal properties. The long-used spermicide nonoxinol-9 (N-9) needs to be replaced for two reasons. First, there is no evidence to show it aids efficacy with condoms[71]. Second, we now know that its surfactant effect can damage lower genital tract epithelial surfaces and thereby possibly increase the risk of acquisition of infections, including HIV[72]. As well as research into spermicides with microbicidal activity, there has also been intensive activity identifying pure microbicides to protect those wanting to achieve pregnancy. Of the former category, two preparations reached the stage of clinical trials for pregnancy prevention. C31G or Savvy (Biosyn, Philapdelphia, PA, USA) is a surfactant which has a satisfactory safety and side effect profile[73]. A phase-3 multicentre RCT of C31G compared to N-9 gel is under way in the USA to investigate its efficacy, safety and acceptability. Cellulose sulfate (Ushercell™: Polydex

Pharmaceuticals Ltd, Toronto, ON, Canada) is a polyanion that inhibits hyaluronidase, induces acrosomal loss and inhibits cervical mucus penetration. In 2007, two phase-3 HIV prevention trials of cellulose sulfate were halted because in one of the trials a trend had been found toward increased HIV risk[74]. A phase-2 contraceptive efficacy study of cellulose sulfate gel conducted in Los Angeles has yet to be reported on. A phase-1 study of the spermicide ACIDFORM applied once daily showed it to be a safe product[75]. A phase-1 study of polystyrene sulfonate gel showed a safety profile comparable with N-9[76].

A phase-1 study has been carried out of a gel composed of polyoxyethylene-polyoxypropylene block copolymer with the microbicide 2% sodium lauryl sulfate[77]. This is applied inside the vagina and acts as both a physical and a chemical barrier. The product was imperceptible to all male partners in the study, potentially empowering women whose partners will not use condoms. A large phase-3 RCT showed that an acid buffering gel, BufferGel, used with a diaphragm was as effective as use with N-9 spermicide[78]. BufferGel is a non-surfactant spermicide which reinforces normal vaginal acidity to inactivate both sperm and acid-sensitive sexually transmitted pathogens. The 6-month pregnancy rate was 10.1% for BufferGel and 12.3% for N-9 users.

Finally, a highly innovative pilot study has examined the vaginal administration of LNG in Carraguard® gel (Population Council, New York, USA) as a potential emergency contraceptive with microbicidal properties[79]. A single vaginal administration of 750mcg LNG in CARRA gel in the late follicular phase was found to be effective in interfering with ovulation. This therefore is a promising method for use as an emergency contraceptive method for occasional use and has the potential for providing dual protection when used before sex thereby putting women more in control. The microbicidal properties of CARRA gel have yet to be demonstrated, but

even if found not to be effective, the principle is established and another microbicide could be substituted.

Male barrier methods

Alternative materials to latex rubber have been developed. These include polyurethane and styrene ethylene butylene styrene (SEBS). Condoms made with these materials have two advantages over latex condoms: a longer shelf-life and the ability to be used in the presence of oil-based lubricants. Synthetic non-latex condoms have a high acceptability and despite being more liable to split or slip off, most are as effective in preventing pregnancy as latex condoms[80].

Female barrier methods

Since the introduction of the original polyurethane female condom (FC1) in 1992, there have been a number of other products tested which incorporate different designs and materials with cost reduction as a major driver. The FC2 female condom is made from synthetic latex which is softer than polyurethane and is manufactured by a dipping process which is cheaper than the welding used in the original type[81]. The VA feminine condom (also known as the Reddy condom and V-Amour) contains a soft sponge to hold it in place inside the vagina rather than a ring; it has a higher acceptability than the FC1[82]. The Program for Approved Technology in Health (PATH) has developed a woman's condom which consists of a dissolvable capsule intended the make insertion easier, a polyurethane condom pouch and a soft outer ring allowing for a nearly universal fit. Once inserted, sections of urethane foam on the condom pouch allow the condom to cling lightly to the vaginal walls so that it does not move during use; acceptability studies are promising[83].

The SILCS diaphragm is being developed by PATH in an iterative process based on a needs assessment and subsequent feedback from users and clinicians. It is a single-size, non-latex diaphragm with a polymer spring. It fits most women without assessment by a health care professional, appears to be more comfortable than existing metal spring devices and can be used with either a spermicide or lubricant. Magnetic resonance imaging in six subjects showed that the diaphragm covered the cervix in all cases and was not dislodged during simulated sex[84]. A phase-1 study of the SILCS diaphragm examined use with either N-9 gel or lubricant only. A reduction in the average number of progressively motile sperm per high power field in the cervical mucus from a baseline of 12.5 to zero was seen when the diaphragm was used with N-9[85]. It has now entered phase-3 trials with randomisation to SILCS diaphragm used with BufferGel or SILCS used with 2% N-9 gel.

The effectiveness of the FC1 is lower than that of male condoms[5]. With all the newer female barrier methods, there is a general dearth of efficacy data.

Male hormonal methods

After two decades of research, there is still no hormonal method for men. Work has focused on hormones that will suppress follicle stimulating hormone and luteinising hormone. Because lack of luteinising hormone leads to atrophy of Leydig cells and testosterone deficiency, exogenous testosterone needs to be added to any regimen. Progress has been painfully slow in this area of research partly because of difficulty finding an appropriate testosterone formulation. To this day, testosterone has to be administered by injection or implants; testosterone in the form of tablets or patches suppresses sperm less effectively.

The most promising regimens are combinations of testosterone with an oral progestogen or progestogen implant[86]. No combination so far has resulted in 95% azoospermia. Due to these small proportions of men who are resistant to hormonal suppression, semen analysis would be needed to identify these individuals if a product were to be launched.

In multicentre male hormonal trials, it was noted that Asian men respond to exogenous androgens with or without progestogens with more suppression of spermatogenesis than non-Asians[86]. Postulated explanations for this have been a more sensitive hypothalamo-pituitary axis, lower testis volume or higher basal apoptotic rate of germ cells in Asian men. Therefore, it is likely that an ethnic or geographical variation exists in the testicular responsiveness to gonadotrophin suppression by exogenous androgens and/or progestogens. Androgen alone contraceptive regimens may be feasible and effective in Asian men, but not in non-Asian men.

Trials in men have been characterised by low numbers of subjects mainly due to low levels of funding. It is disappointing that both pharmaceutical companies that have been funding male hormonal methods have decided to withdraw from this field of research[87]. Reasons for this decision would appear to be perceived poor profitability in the context of a shrinking global market and the possibility of legal suit from men for whom the method fails. Nevertheless, there is still support from WHO and Contraceptive Research and Development Program.

Vaccines

Despite extensive efforts, the quest for a contraceptive vaccine has been largely unsuccessful so far[88]. Only one vaccine has gone through phase-2 trials, an anti-

human chorionic gonadotrophin vaccine[89]. This vaccine gives contraceptive protection to some women, but it generates above protective threshold titres in only 60 – 80% of women.

Female sterilisation

Mechanical devices such as plugs and thermal occlusion have been investigated with limited success and some adverse effects. Two so-called hybrid methods have been much more successful.

Essure® (Conceptus Inc, San Carlos, CA, USA) is a metallic and fibre microcoil device inserted through the ostia of the Fallopian tubes using a 5-French gauge hysteroscope. The inner coil is stainless steel and the outer coil nickel titanium alloy. Woven throughout the inner coil are polyethylene terephthalate fibres. The device is delivered into the tube in a tightly wound position. When in situ the device is released so that the rapidly expanding outer coil fills the tubal lumen, anchoring the device. Fibrosis occurs into and around the microcoil, providing an irreversible method. Specific training in its insertion is necessary. Placement has to be confirmed, usually by X-ray or ultrasound imaging three months after the procedure. Placement failure occurs in about 6% of cases[90]. In women with correctly placed devices, bilateral tubal occlusion is demonstrated in 99.5% of women at 12 months. A pregnancy rate of 1.2 per 1000 has been reported to the device manufacturer in an analysis of 64 pregnancies out of an estimated 50 000 procedures carried out between 1997 and 2005[91]. The procedure can be performed in a treatment room setting, with no need for operating theatre facilities[92]. However, UK National Institute for Health and Clinical Excellence guidance is still that this procedure should only be performed with special arrangements for consent and for audit and research[93]. In a recent case series report, three tubal perforations were described in 143 consecutive insertions[94].

Adiana® (Hologic Inc, Bedford, MA, USA) is a two-step procedure comprising controlled thermal damage of the endosalpinx followed by insertion of a biocompatible matrix plug within the tubal lumen. Results in trials are encouraging[95].

Women need a full explanation about hybrid methods regarding their complete irreversibility but their greater safety, as the abdomen is not entered.

Male sterilisation

Reversible inhibition of sperm under guidance (RISUG) is a clear polymer gel made of styrene maleic anhydride mixed with dimethyl sulfoxide which has been developed in India. RISUG is injected into the vas and then solidifies; it appears to cause partial obstruction of the vas while also causing the membranes of passing sperm to rupture. Phase-2 trials show that users have azoospermia or non-motile sperm for at least one year[96]. Further toxicology studies are awaited.

The intra vas device (Shepherd Medical, Minneapolis, MN, USA) is implanted into the vas. It consists of two flexible silicone plugs per vas; these are joined by a thread which remains outside the vas that is used to remove the device. The method is slightly less likely to cause azoospermia than no-scapel vasectomy but delayed complications are less frequent[97].

The VasClip (VasClip, Roseville, MN, USA) is a small polymeric clip applied to the vas. In a phase-2 study, 116 of 119 subjects were azoospermic at 10 – 14 months after the procedure[98]. Sperm granuloma formation incidence was low and acceptability high.

Conclusions

There are more than a dozen existing methods of contraception, all except two designed for women. New methods rely on varying existing technology. The development of male hormonal methods has been set back by withdrawal of pharmaceutical company support. One has to question the philosophy of the pharmaceutical industry in not comprehensively supporting research in contraception, which can do so much to promote reproductive rights and to relieve suffering of millions of women and their families worldwide.

Although some new oestrogen and progestogen hormones have been synthesised, greater progress has been made in developing new delivery systems. Hormones can now be delivered via six different routes: oral, injectable, implantable, vaginal, transdermal and intrauterine. The development of hormone-containing controlled – release polymers has allowed steady hormone levels to be maintained for several years.

Mifepristone has great potential as an oral contraceptive and emergency contraceptive agent, but it would appear that industry is unlikely to invest in this as opposition from the public and politicians would be likely to undermine product development. A possible solution to this is the development of PRMs without abortifacient properties.

Disclosure of interests

The author attended the 10th European Society of Contraception Congress in Prague in 2008 at the invitation of Schering-Plough Ltd.

Funding

None.

Word count: 5392 including abstract but excluding references

Reference List

(1) Singh S, Darroch JE, Vlassoff M, Nadeau J. Adding it up: the benefits of investing in sexual and reproductive health care. New York: Guttmacher Institute/UNFPA; 2003.

(2) World contraceptive use [http://www.un.org/esa/population/unpop.htm]. United Nations; 2008.

(3) Lader D. Contraception and sexual health 2006/07. Newport: Office for National Statistics; 2007.

(4) National Collaborating Centre for Women's and Children's Health. Long-acting reversible contraception (NICE guideline). London: RCOG [http://www.nice.org.uk]; 2005.

(5) Trussell J. Contraceptive efficacy. In: Hatcher RA, Trussell J, Nelson AL, Cates W, Stewart FH, Kowal D, editors. Contraceptive technology. 19th ed. New York: Ardent Media; 2007. 747-826.

(6) Belfield T. Contraception: users' perspectives and determinants of choice. In: Glasier A, Wellings K, Critchley H, editors. Contraception and contraceptive use. London: RCOG Press; 2005. 78-87.

(7) Heinemann K, Saad F, Wiesemes M, White S, Heinemann L. Attitudes toward male fertility control: results of a multinational survey on four continents. Hum Repro 2005; 20:549-556.

(8) Glasier AF, Anakwe R, Everington D, Martin CW, van der Spuy Z, Cheng L et al. Would women trust their partners to use a male pill? Hum Repro 2000; 15:646-649.

(9) Rowlands S. Newer progestogens. J Fam Plann Reprod Health Care 2003; 29:13-16.

(10) Sitruk-Ware R. New progestagens for contraceptive use. Human Reproduction Update 2006; 12:169-178.

(11) Wiegratz I, Lee JH, Kutschera E, Winkler UH, Kuhl H. Effect of four oral contraceptives on hemostatic parameters. Contraception 2004; 70:97-106.

(12) Endrikat J, Parke S, Trummer D, Schmidt W, Duijkers I, Klipping C. Ovulation inhibition with four variations of a four-phasic estradiol valerate/dienogest combined oral contraceptive: results of two prospective, randomized, open-label studies. Contraception 2008; 78:218-225.

(13) Parke S, Makalova D, Ahrendt H-J, Mansour D. Bleeding patterns and cycle control with a novel four-phasic combined oral contraceptive containing estradiol valerate and dienogest. European Journal of Contraception & Reproductive Health Care 13 (Suppl 2), 94-95. 2008.
Ref Type: Abstract

(14) Visser M, Coelingh Bennink H. Estetrol: a new estrogen in the pill? European Journal of Contraception & Reproductive Health Care 13 (Suppl

2), 17. 2008.
Ref Type: Abstract

(15) Archer DF. Menstrual-cycle-related symptoms: a review of the rationale for continuous use of oral contraceptives. Contraception 2006; 74:359-366.

(16) Miller L, Hughes JP. Continuous combination oral contraceptive pills to eliminate withdrawal bleeding: a randomized trial. Obstet Gynecol 2003; 101:653-661.

(17) Anderson FD, Gibbons W, Portman D. Long-term safety of an extended-cycle oral contraceptive (Seasonale): a 2-year multicenter open-label extension trial. Am J Obstet Gynecol 2006; 195:92-96.

(18) Archer DF, Jensen JT, Johnson JV, Borisute H, Grubb GS, Constantine GD. Evaluation of a continuous regimen of levonorgestrel/ethinyl estradiol: phase 3 study results. Contraception 2006; 74:439-445.

(19) Willis SA, Kuehl TJ, Spiekerman AM, Sulak PJ. Greater inhibition of the pituitary-ovarian axis in oral contraceptive regimens with a shortened hormone-free interval. Contraception 2006; 74:100-103.

(20) Nakajima ST, Archer DF, Ellman H. Efficacy and safety of a new 24-day oral contraceptive regimen of norethindrone acetate 1 mg/ ethinyl estradiol 20 microg (Loestrin 24 Fe). Contraception 2007; 75:16-22.

(21) Fenton C, Wellington K, Moen MD, Robinson DM. Drospirenone/ethinylestradiol 3mg/20microg (24/4 day regimen): a review of its use in contraception, premenstrual dysphoric disorder and moderate acne vulgaris. Drugs 2007; 67:1749-1765.

(22) Lakha F, Ho PC, Van der Spuy ZM, Dada K, Elton R, Glasier AF et al. A novel estrogen-free oral contraceptive pill for women: multicentre, double-blind, randomized controlled trial of mifepristone and progestogen-only pill (levonorgestrel). Hum Repro 2007; 22:2428-2436.

(23) Pei K, Xiao B, Jing X, Lu S, Wei L, Zhao H. Weekly contraception with mifepristone. Contraception 2007; 75:40-44.

(24) Chabbert-Buffet N, Pintiaux-Kairis A, Bouchard P. Effects of the progesterone receptor modulator VA2914 in a continuous low dose on the hypothalamic-pituitary-ovarian axis and endometrium in normal women: a prospective, randomized, placebo-controlled trial. J Clin Endocrinol Metab 2007; 92:3582-3589.

(25) Den Tonkelaar I, Oddens BJ. Preferred frequency and characteristics of menstrual bleeding in relation to reproductive status, oral contraceptive use, and hormonal replacement therapy use. Contraception 1999; 59:357-362.

(26) Glasier AF, Smith KB, Van der Spuy ZM, Ho PC, Cheng L, Dada K et al. Amenorrhoea associated with contraception: an international study on acceptability. Contraception 2003; 67:1-8.

(27) Task Force on Postovulatory Methods of Fertility Regulation. Comparison of three single doses of mifepristone as emergency contraception: a randomised trial. Lancet 1999; 353:697-702.

(28) von Hertzen H, Piaggio G, Ding J, Chen J, Song S, Bártfai G et al. Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomised trial. Lancet 2002; 360:1803-1810.

(29) Creinin MD, Schlaff W, Archer DF, Wan L, Frezieres R, Thomas M et al. Progesterone receptor modulator for emergency contraception: a randomized controlled trial. Obstet Gynecol 2006; 108:1089-1097.

(30) Gemzell-Danielsson K, Marions L. Mechanisms of action of mifepristone and levonorgestrel when used for emergency contraception. Human Reproduction Update 2004; 10:341-348.

(31) Novikova N, Weisberg E, Stanczyk FZ, Croxatto HB, Fraser IS. Effectiveness of levonorgestrel emergency contraception given before or after ovulation - a pilot study. Contraception 2007; 75:112-118.

(32) Massai MR, Forcelledo ML, Brache V, Tejada AS, Salvatierra AM, Reyes MV et al. Does meloxicam increase the incidence of anovulation induced by single administration of levonorgestrel in emergency contraception? A pilot study. Hum Repro 2007; 22:434-439.

(33) Pall M, Friden BE, Brannstrom M. Induction of delayed follicular rupture in the human by the selective COX-2 inhibitor rofecoxib: a randomized double-blind study. Hum Repro 2001; 16:1323-1328.

(34) Kaunitz AM, Arias R, McClung M. Bone density recovery after depot medroxyprogesterone acetate injectable contraception use. Contraception 2008; 77:67-76.

(35) Jain J, Jakimiuk AJ, Bode FR, Ross D, Kaunitz AM. Contraceptive efficacy and safety of DMPA-SC. Contraception 2004; 70:269-275.

(36) Prabhakaran S. Self-administration of injectable contraceptives. Contraception 2008; 77:315-317.

(37) Sang GW, Shao QX, Ge RS, Ge JL, Chen JK, Song S et al. A multicentred phase III comparative clinical trial of Mesigyna, Cyclofem and Injectable No. 1 given monthly by intramuscular injection to Chinese women 1. Contraceptive efficacy and side effects. Contraception 1995; 51:167-183.

(38) Rahimy MH, Ryan KK. Lunelle monthly contraceptive injection (medroxyprogestone acetate and estradiol cypionate injectable suspension): assessment of return of ovulation after three monthly injections in surgically sterile women. Contraception 1999; 60:189-200.

(39) Hall PE. New once-a-month injectable contraceptives, with particular reference to Cyclofem/Cyclo-Provera. Int J Gynecol Obstet 1998; 62 Suppl 1:S43-S56.

(40) Stanwood NL, Eastwood K, Carletta A. Self-injection of monthly combined hormonal contraceptive. Contraception 2006; 73:53-55.

(41) Sivin I, Mishell DR, Alvarez F, Brache V, Elomaa K, Lahteenmaki P et al. Contraceptive vaginal rings releasing Nestorone and ethinylestradiol: a 1-year dose-finding trial. Contraception 2005; 71:122-129.

(42) Novák A, de la Loge C, Abetz L, van der Meulen EA. The combined contraceptive vaginal ring, NuvaRing: an international study of user acceptability. Contraception 2003; 67:187-194.

(43) vanden Heuvel MW, van Bragt AJM, Alnabawy AKM, Kaptein MCJ. Comparison of ethinylestradiol pharmacokinetics in three hormonal contraceptive formulations: the vaginal ring, the transdermal patch and an oral contraceptive. Contraception 2005; 72:168-174.

(44) Oddsson K, Leifels-Fischer B, de Melo NR, Wiel-Masson D, Benedetto C, Verhoeven CHJ et al. Efficacy and safety of a contraceptive vaginal ring (NuvaRing) compared with a combined oral contraceptive: a 1-year randomized trial. Contraception 2005; 71:176-182.

(45) Ahrendt H-J, Nisand I, Bastianelli C, Gomez MA, Gemzell-Danielsson K, Urdl W et al. Efficacy, acceptability and tolerability of the combined contraceptive ring, NuvaRing, compared with an oral contraceptive containing 30 µg ethinyl estradiol and 3 mg of drospirenone. Contraception 2006; 74:451-457.

(46) Bjarnadóttir RI, Tuppurainen M, Killick SR. Comparison of cycle control with a combined contraceptive vaginal ring and oral levonorgestrel/ethinyl estradiol. Am J Obstet Gynecol 2002; 186:389-395.

(47) Oddson K, Leifels-Fischer B, Wiel-Masson D, de Melo NR, Benedetto C, Verhoeven CH et al. Superior cycle control with a contraceptive vaginal ring compared with an oral contraceptive containing 30mcg ethinylestradiol and 150mcg levonorgestrel: a randomized trial. Hum Repro 2005; 20:557-562.

(48) Roumen FJME, op ten Berg MMT, Hoomans EHM. The combined contraceptive ring (NuvaRing): first experience in daily clinical practice in the Netherlands. European Journal of Contraception & Reproductive Health Care 2006; 11:14-22.

(49) Merki-Feld GS, Hund M. Clinical experience with NuvaRing in daily practice in Switzerland: cycle control and acceptability among women of all reproductive ages. European Journal of Contraception & Reproductive Health Care 2007; 12:240-247.

(50) Massai R, Quinteros E, Reyes MV, Caviedes R, Zepeda A, Montero JC et al. Extended use of a progesterone-releasing vaginal ring in nursing women: a phase II clinical trial. Contraception 2005; 72:352-357.

(51) Brache V, Mishell DR, Lahteenmaki P, Alvarez F, Elomaa K, Jackanicz T et al. Ovarian function during use of vaginal rings delivering three different doses of Nestorone®. Contraception 2001; 63:257-261.

(52) Croxatto HB, Brache V, Massai R, Alvarez F, Forcelledo ML, Pavez M et al. Feasibility study of Nestorone®-ethinylestradiol vaginal contraceptive ring for emergency contraception. Contraception 2006; 73:46-52.

(53) Sivin I, Campodonico I, Kiriwat O, Holma P, Diaz S, Wan L et al. The performance of levonorgestrel rod and Norplant contraceptive implants: a 5 year randomized study. Hum Repro 1998; 13:3371-3378.

(54) Newton J, Newton P. Implanon® - the single-rod subdermal contraceptive implant. J Drug Eval 2003; 1:181-218.

(55) Sivin I, Croxatto H, Bahamondes L, Brache V, Alvarez F, Massai R et al. Two-year performance of a nestorone-releasing contraceptive implant: a three-center study of 300 women. Contraception 2004; 69:137-144.

(56) Barbosa IC, Maia H, Coutinho E, Lopes R, Lopes AC, Noronha C et al. Effects of a single silastic contraceptive implant containing nomegestrol acetate (Uniplant) on endometrial morphology and ovarian function for 1 year. Contraception 2006; 74:492-497.

(57) Darney PD, Klaisle CM, Monroe SE, Cook CE, Phillips NR, Schindler A. Evaluation of a 1-year levonorgestrel-releasing contraceptive implant: side effects, release rates and biodegradability. Fertil Steril 1992; 58:137-143.

(58) Raymond EG, Singh M, Archer DF, Saxena BB, Baker J, Cole D. Contraceptive efficacy, pharmacokinetics and safety of Annuelle biodegradable norethindrone pellet implants. Fertil Steril 1996; 66:954-961.

(59) Audet MC, Moreau M, Koltun WD, Waldbaum AS, Shangold G, Fisher AC et al. Evaluation of contraceptive efficacy and cycle control of a transdermal contraceptive patch vs an oral contraceptive: a randomized controlled trial. JAMA 2001; 285:2347-2354.

(60) Zieman M, Guillebaud J, Weisberg E, Shangold GA, Fisher AC, Creasy GW. Contraceptive efficacy and cycle control with the Ortho Evra™/Evra™ transdermal system: the analysis of pooled data. Fertil Steril 2002; 77 (Suppl 2):S13-S18.

(61) Heger-Mahn D, Warlimont C, Faustmann T, Gerlinger C, Klipping C. Combined ethinylestradiol/gestodene contraceptive patch: two-center, open-label study of ovulation inhibition, acceptability and safety over two cycles in female volunteers. European Journal of Contraception & Reproductive Health Care 2004; 9:173-181.

(62) Sitruk-Ware R, Small M, Kumar N, Tsong YY, Sundaram K, Jackanicz T. Nestorone: clinical applications for contraception and HRT. Steroids 2003; 68:907-913.

(63) Fraser IS, Weisberg E, Kumar N, Kumar S, Humberstone AJ, McCrossin L et al. An initial pharmacokinetic study with a metered dose transdermal system for the delivery of the progestogen nestorone as a possible future contraceptive. Contraception 2007; 76:432-438.

(64) Clinical Effectiveness Unit. Intrauterine contraception. 2nd ed. London: Faculty of Sexual & Reproductive Healthcare [http://www.fsrh.org]; 2007.

(65) Sivin I. Utility and drawbacks of continuous use of a copper T IUD for 20 years. Contraception 2007; 75:S70-S75.

(66) Kulier R, O'Brien P, Helmerhorst F, Usher-Patel M, d'Arcangues C. Copper containing, framed intra-uterine devices for contraception. Cochrane Database of Syst Rev 2007; 4: CD005347.

(67) UNDP, UNFPA, WHO Special Programmes of Research DaRTiHR, World Bank: IUD Research Group. The TCu 380A IUD and the frameless IUD "the FlexiGard": interim three-year data from an international multicenter trial. Contraception 1995; 52:77-83.

(68) Wildemeersch D, Janssens D, Vrijens M, Weyers S. Ease of insertion, contraceptive efficacy and safety of new T-shaped levonorgestrel-releasing intrauterine system. Contraception 2005; 71:465-469.

(69) Wildemeersch D, Schacht E, Wildemeersch P. Contraception and treatment in the perimenopause with a novel "frameless" intrauterine levonorgestrel-releasing drug delivery system: an extended pilot study. Contraception 2002; 66:93-99.

(70) Batár I. State-of-the-art of intrauterine contraception. European Journal of Contraception & Reproductive Health Care 2006; 11:262-269.

(71) Anonymous. WHO/CONRAD technical consultation on nonoxynol-9. Geneva: World Health Organisation; 2002.

(72) Hillier SL, Moench T, Shattock R, Black R, Reichelderfer P, Veronese F. In vitro and in vivo: the story of nonoxynol 9. J Acquir Immune Defic Syndr 2005; 39:1-8.

(73) Mauck CK, Weiner DH, Creinin MD, Barnhart KT, Callahan MM, Bax R. A randomized Phase I vaginal safety study of three concentrations of C31G vs. extra strength Gynol II. Contraception 2004; 70:233-240.

(74) van der Wijgert JHHM, Shattock RJ. Vaginal microbicides: moving ahead after an unexpected setback. AIDS 2007; 21:2369-2376.

(75) Amaral E, Perdigao A, Souza MH, Mauck C, Waller D, Zaneveld L et al. Vaginal safety after use of a bioadhesive acid-buffering, microbicidal contraceptive gel (ACIDFORM) and a 2% nonoxynol-9 product. Contraception 2006; 73:542-547.

(76) Mauck CK, Weiner DH, Ballagh SA, Creinin MD, Archer DF, Schwartz JL et al. Single and multiple exposure tolerance study of polystyrene sulfonate gel: a phase I safety and colposcopy study. Contraception 2004; 70:77-83.

(77) Trottier S, Omar RF, Désormeaux A, Drouin J, Gagnon M-T, Vezina F et al. Safety, tolerance and acceptability of the Invisible Condom® and its vaginal applicator in healthy women and their sexual partners. Contraception 2007; 76:117-125.

(78) Barnhart KT, Rosenberg MJ, MacKay HT, Blithe DL, Higgins J, Walsh T et al. Contraceptive efficacy of a novel spermicidal microbicide used with a

diaphragm: a randomized controlled trial. Obstet Gynecol 2007; 110:577-586.

(79) Brache V, Croxatto H, Sitruk-Ware R, Maguire R, Montero JC, Kumar N et al. Effect of a single vaginal administration of levonorgestrel in Carraguard® gel on the ovulatory process: a potential candidate for "dual protection" emergency contraception. Contraception 2007; 76:111-116.

(80) Gallo MF, Grimes DA, Lopez LM, Schulz KF. Non-latex versus latex male condoms for contraception. Cochrane Database of Syst Rev 2006; (1): CD003550.

(81) Beksinska M, Smit J, Mabude Z, Vijayakumar G, Joanis C. Performance of the Reality® polyurethane female condom and a synthetic latex prototype: a randomized crossover trial among South African women. Contraception 2006; 73:386-393.

(82) Smita J, Neelam J, Rochelle DY, Kumar BK, Callahan M, Suniti S et al. Comparative acceptability study of the Reality female condom and the version 4 of modified Reddy female condom in India. Contraception 2005; 72:366-371.

(83) Coffey PS, Kilbourne-Brook M, Austin G, Seamans Y, Cohen J. Short-term acceptability of the PATH woman's condom among couples at three sites. Contraception 2006; 73:588-593.

(84) Yang CC, Maravilla KR, Kilbourne-Brook M, Austin G. Magnetic resonance imaging of SILCS diaphragm: anatomical considerations and corroboration with clinical fit. Contraception 2007; 76:238-244.

(85) Schwartz JL, Ballagh SA, Creinin MD, Rountree RW, Kilbourne-Brook M, Mauck CK et al. SILCS diaphragm: postcoital testing of a new single-size contraceptive device. Contraception 2008; 78:237-244.

(86) Wang C, Swerdloff RS. Male hormonal contraception. Am J Obstet Gynecol 2004; 190:S60-S68.

(87) Liu PY, McLachlan RI. Male hormonal contraception: so near and yet so far. J Clin Endocrinol Metab 2008; 93:2474-2476.

(88) Naz RK, Gupta SK, Gupta JC, Vyas HK, Talwar GP. Recent advances in contraceptive vaccine development: a mini-review. Hum Repro 2005; 20:3271-3283.

(89) Talwar GP, Singh O, Gupta SK, Hasnain SE, Pal R, Majumdar SS et al. The HSD-hCG vaccine prevents pregnancy in women, feasibility studies of reversible safe contraception vaccine. Am J Reprod Immunol 1997; 37:153-160.

(90) Sagili H, Divers M. Hysteroscopic sterilisation with Essure®: a promising new alternative to tubal ligation? J Fam Plann Reprod Health Care 2008; 34:99-102.

(91) Levy B, Levie MD, Childers ME. A summary of reported pregnancies after hysteroscopic sterilization. J Minim Invasive Gynecol 2007; 14:271-274.

(92) Nichols M, Carter JF, Fylstra DL, Childers M. A comparative study of hysteroscopic sterilization performed in-office versus a hospital operating room. J Minim Invasive Gynecol 2006; 13:447-450.

(93) Anonymous. Hysteroscopic sterilisation by tubal cannulation and placement of intrafallopian implants. Interventional Procedure Guidance 44. London: National Institute for Clinical Excellence [http://www.nice.org.uk]; 2004.

(94) Langenveld J, Veersema S, Bongers MY, Koks CA. Tubal perforation by Essure: three different clinical presentations. Fertil Steril 2008; (in press).

(95) Johns D. Advances in hysteroscopic sterilization: report on 600 patients enrolled in the Adiana EASE pivotal trial. J Minim Invasive Gynecol 2005; 12 (Suppl):S39-S40.

(96) Guha SK, Singh G, Srivastava A, Das HC, Bhardwaj JC, Mathur V et al. Two-year clinical efficacy trial with dose variations of a vas deferens injectable contraceptive for the male. Contraception 1998; 58:165-174.

(97) Song L, Gu Y, Lu W, Liang X, Chen Z. A phase II randomized controlled trial of a novel male contraception, an intra vas device. Int J Andrology 2006; 29:489-495.

(98) Kirby D, Utz WJ, Parks PJ. An implantable ligation device that achieves male sterilisation without cutting the vas deferens. Urology 2006; 67:807-811.