



Long-Acting Reversible Contraceptives - IUDs/IUS and Implants: A Review

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ABSTRACT

Unexpected or unintended pregnancy is a global health concern. Young women who are pregnant are refused contraception care in many nations. For women, reversible methods of contraception with long-acting methods such as intrauterine devices (IUDs) proved more productive than short-acting methods including tablets and condoms. We systematically searched on Google scholar, PubMed, LitCovid, and MedRxiv using the search terms unintended pregnancy, contraception, implants, and IUD/IUS for published articles. The available IUDs now provide nearly complete childbirth protection although have few complications. Implantable contraceptives are commonly practiced all around the globe. Implants are among the most effective and reliable contraceptive strategies available. The Food and Drug Administration (FDA) of the United States in 1990, approved the Norplant contraceptive. The IUDs and implants apart from being successful contraceptives have a variety of harmful effects, which led the development in the field. The insertion and removal involving a qualified individual and the aseptic setting were correlated with other small hazards for IUDs and implants. This review focuses on the complications with IUDs and implants, and also focuses on the developments in the field of novel IUDs approaches.

Keywords: Pregnancy, Contraception, Intrauterine devices, Implants, Childbirth, Harmful effects.

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INTRODUCTION

Long-acting reversible contraceptives (LARCs) are those methods that provide effective birth control for a longer time span and with less hassle, as these methods do not require dynamic adherence, these are user-independent methods which do not require intervention unless it is needed to discontinue¹. A somewhat less commonly used term for these contraceptives is forgettable contraception, which are those techniques that do need observance no more often than every 3 years which include intrauterine devices, implants as well as sterilization². Amidst women in the United States (US), the utilization of LARC's has increased from 2.4% to 11.6% from 2002 to 2012³. Unintended pregnancies, as well as abortions, were reduced during this span⁴. Most commonly used short-acting contraceptives such as oral pills, condoms, diaphragms, etc, have limited efficiency because of high failure rate and low resumption rate whereas LARCs have low discontinuation rates and low failure^{1,5}. LARCs are getting popular because of extensive chances to access⁶. Intrauterine devices (IUDs) can be hormonal such as levonorgestrel intrauterine systems (LNG-IUS) and non-hormonal such as copper IUDs

as well as etonogestrel implants are types of LARCs, implants are approved for continuous use for 3 years². Contraceptive implants have lesser acceptability because of interference in menses⁷. IUDs are highly efficacious in the prevention of pregnancy and cost-beneficial thus these are maximally used LARCs in the world which is extremely popular in Europe⁸. Specifically, for contraception in 1909, the first intrauterine device was promoted, it was produced from silkworm gut configured as a ring⁹. Over 200 million women worldwide use copper IUD, it is highly effective in emergency contraception, but it has some complications associated with it like pain and hemorrhage which needs improvement. LNG-IUS lowers period flow and reduces painful menstruation, contrary to copper IUD which elevates menstrual discharge¹⁰.

Globally, implantable contraceptives are commonly practiced. Implants are one of the most efficient and reversible models of contraceptive accessibility. These tools may be useful for many female populations, particularly females those can't use estrogen-containing contraceptives. For females with many chronic medical conditions, implants are safe to use¹¹. Contraceptive implants provide tremendous potential for planning the family. Currently, more than 220 million females have unmet demand for modern contraceptives in growing countries, majorly in South Asia, and Sub-Saharan Africa¹². About a third and a half of deliveries are considered unintended in several high-income countries. Many of these unplanned pregnancies happen when contraceptive measures, such as pills and condoms, are less effective. Further LARCs uptake is expected to reduce unplanned pregnancy¹³.



TYPES OF IUDS AND THEIR MECHANISM OF ACTION

The creation of the T-shaped device, a model that is more suitable for the normal structure of the uterus, was the basis for the new IUDs in the 1960s. In the 1960s, the benefits of the IUDs proved to be easier to use than the commonly available contraceptive, and the possible cardiovascular risks were smaller. Around 10% of women who use contraceptives choose an IUD by the 1970s¹⁴. Primarily Intrauterine devices are of two types: Copper IUDs and hormonal IUDs. However other IUDs are in development or clinical trials for their efficacy and safety.

I. Copper IUDs

With various copper wirings, copper consisting IUDs are wrapped up to provide closer proximity of copper surface to the uterine fundus, there is commonly inclusion of copper in the horizontal arm and vertical stem, for copper IUDs, three to seven years of the span is suggested for its use¹⁵. The importance of the copper surface area has been found in the studies which were conducted in the 1970s that is more is the copper surface of IUDs, lesser is the rate of failure¹⁶. TCu380A copper IUD has approval for 10-year of constant use by US-FDA, it is used extensively around the globe and is considered as one of the most efficacious copper IUD¹⁵. This IUD declines the susceptibility to pregnancy to 1 in 1000 if inserted, between five-seven days of vulnerable intercourse¹⁷. Various randomized clinical trials conducted by the world health organization (WHO), to assess the efficacy of Nova T, TCu380A, and Multiload Cu250 out of which cumulative pregnancy rate was least for Cu380A¹⁸.

Absolute toxicity is a fundamental mode of action of IUDs by which fertilization is hindered. Pre- and post-fertilization effects add to IUDs' effectiveness which has been reported in a systematic review¹⁹. Cu-IUDs have a fundamental mode of action, to make spermatozoa inoperative by corrosion of copper releasing copper ions in the result of it²⁰. Copper ions released from copper IUD has an immobilizing effect on sperms and effect on viability as well, the effectiveness of the device is supported by the alterations in the mucus of the cervical region and lymphocytes engagement²¹. Spermatozoa penetration is constrained by changes in copper concentration of cervical mucus²². Copper IUDs activate the foreign body reaction for spermatozoa passing through the mucus of the cervical region²³.

II. Hormonal Intrauterine devices

IUS are implanted into the uterine cavity to prohibit pregnancy, Because of greater competence, patient compliance, these devices are widely used LARCs. As per clinical trials conducted, 52 mg LNG-IUS showed the rate of pregnancy at the tenure of 1st year of usage to be 0.2-0.3% and LNG-IUS is given due consideration to be the utmost efficacious IUDs accessible²⁴. Mirena is the first LNG-IUS which received approval for 5 years of use, Hormonal IUDs are accessible to use since 1976^{25,26}. From 2001 to 2015 Mirena was only available IUS with 5-year

approval²⁷. This device is configured on the Nova-T frame, which is 32 mm in length and breadth, the stem of this device constitutes a hormone depot surrounded by a rate-releasing membrane, it releases 20µg of hormone LNG daily, then by year edge 18µg/day and 5µg/day after five years²⁸. Another device that has similarities, in shape, size and hormonal content is Liletta. It was introduced with approval tenure of 3 years but several clinical trials, report the efficiency of the device up to 7 years²⁹. A smaller light 13.5 mg IUS named Skyla by Bayer in the United States and different regions worldwide having approval for three years³⁰.

Hormonal IUDs works by, mucus present in the cervical region is congealed, to stop spermatozoa from moving into the uterus by the device LNG-IUS mitigates endometrium and atrophy and decidualization of endometrium leads to reduced flow of menstruation^{31,32}. Figure 1 represents the usage of IUDs in women between 15 to 44 years of age from 1995 to 2017.

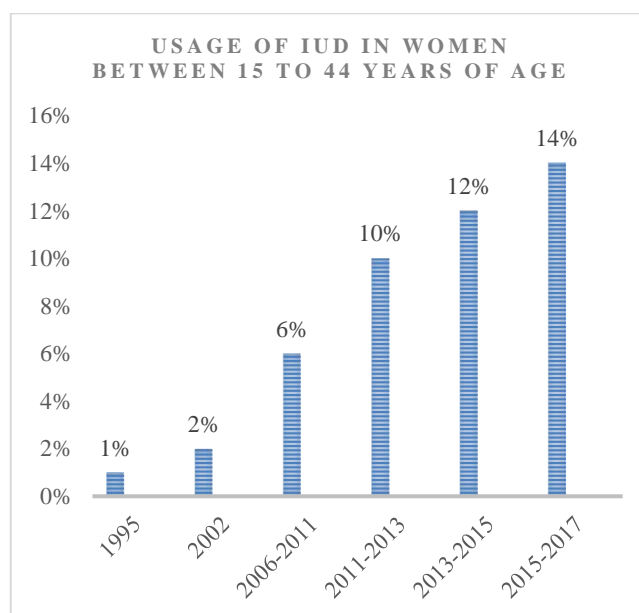


Figure 1: Shows the usage of IUDs in women aged 15-44 years from 1995 to 2017.

COMPLICATIONS

IUD's are not the flawless contraceptives, these contradicted in many health conditions of women like cervix cancer, heart ailment like congenital heart diseases. At the time of IUDs insertion or after some duration, these complications can arise³³.

Pelvic inflammatory disease:

Pelvic inflammatory disease (PID) is a condition of inflammation of infection in the lower genital tract may produce tubal and endometrial infections and its consequence including turbo-ovarian adhesions and tubo ovarian abscess³⁴. In earlier times, PIDs risk was associated with IUDs, which lead to their decreased use³⁵. The escalated occurrence of PID infections is because the IUD increases the vulnerability of the host. The endometrial cavity can get infected with the Bacteria by the

introduction of IUDs. Bacteria can be carried away by the end unit of IUD to the uterus and it can lead to PIDs³⁶. In a study conducted on women age 15-44 years, it was found that IUD users have five times the risk of contracting febrile PIDs than non-IUD users. PID is recorded to be 0 to 8% after IUD insertion³⁷. Another follow-up study showed that there was only a 0 to 0.3 % rate of PID per year which means per 100 women there were 3.5 cases of PID³⁸. The possibility of PIDs is greatly reduced with the latest IUDs, opposite to what was perceived before at least in zones where the occurrence of sexually transmitted diseases (STDs) is less as well as where medical guidance is strictly adhered to. Prevalence of PIDs is more in those regions where there are more cases of the STDs as well as non-maintenance of hygienic conditions during the insertion of the IUDs³⁹.

Uterine perforation:

One of the infrequent but considerable complications of IUDs is a uterine perforation that often arises during IUDs insertion and can happen later on as well⁴⁰. Aspects related to this complication are poor insertion technique, post-partum span as well as lactation. A recently conducted study, found occurrence rates for perforation to be 0.4/1000 insertions with copper IUDs as well as for Hormonal LNG-IUS⁴¹. Whereas in the preceding studies the perforation occurrence rates are 0.4-2.2/1000 insertions in the case of Cu-IUDs and LNG-IUS with 2.6/1000 insertions⁴². Perforations linked to IUDs have abdominal surgery as accepted treatment by laparotomy, which is now replaced by laparoscopic techniques that are safer. As per the case studies the bowel perforations are associated with wrongly placed IUDs⁴³. In disparity to case reports which show hazardous indications larger studies imply that most of IUD linked perforations are related to signs such as light pain or abdominal bleeding or both, collaborated with missed threads or unintentional gestation. As per the latest publications, it's found that perforations are seldom dangerous with current devices being used^{44,45}.

Expulsion:

IUDs expulsion is a frequent complication and it arises in 10% of the patients. Risk factors for expulsion comprise menorrhagia, the instantaneous post-partum introduction of the device, and parity of the patient⁴⁶. Those patients are at a greater likelihood of IUDs expulsion having critical distortions of the uterine cavity⁴⁷. Whether the uterus is retroverted or anteverted, it does not influence expulsion frequency⁴⁸. IUDs expulsion may be asymptomatic or may be correlated with bleeding, pain, or palpation of IUDs in the vagina. Greater accidental pregnancy is related to IUDs, present in the cervical region in comparison to IUDs, which is correctly placed⁴⁹.

Displacement:

It is also a common complication associated with IUDs. In this case, IUD is displaced within the uterine cavity. In 25% of women with IUDs-insertion displacement can arise^{46,50}.

Displaced IUDs, is generally having no symptoms, but some patients may suffer from pain and bleeding. The more is the displacement of the device from its correct position, more is the probability of having less efficacious contraception and greater is the possibility of expulsion. Treatment for this complication can differ among different practitioners and in many instances, rely on the preferences of the patient⁵¹.

Ectopic Pregnancy:

As per the summary of the literature, Tatum and Schmidt report that 4% of pregnancies were ectopic and arose when IUDs were already set up⁵². The multi-center case-control study, that is women health study (WHS) including women of age 18 - 44 with ectopic pregnancy detection concludes that ectopic pregnancy risk is the same for non-user as well as users of IUDs-contraceptives including, IUD decreases the probability of ectopic pregnancy whereas, amidst the present users of IUDs, the risk of ectopic pregnancy is thrice as the user of the oral contraceptives but similar prospect with the conventional contraceptives. Oral contraceptives generally suppress the ovulation that is why on transitioning from IUD to oral contraceptives probability of ectopic pregnancy occurring is reduced⁵³.

Bleeding and pain:

Usually, IUDs are withdrawn because of the problem of bleeding and pain. Bleeding is the reason for more withdrawals than pain³³. As per an investigation, biochemical functions are affected by components of IUDs like water-soluble components and plastic which is the reason why IUDs may cause bleeding⁵⁴. Moreover, IUDs induced bleeding is also caused by mechanical stress induced by a device on endometrium⁵⁵. After insertion of IUDs, menstrual flow may increase, and it may stay for a longer duration, insertion may be associated by pain or cramps, and in some cases, pain can arise even after a long time of insertion³³.

NON-CONTRACEPTIVE BENEFITS OF IUDs

The non-contraceptive benefits of IUDs were not well known before but are getting recognized now. Case-control studies provide ample confirmation that non-medicated or copper IUDs safeguards against endometrial cancer. Regarding endometriosis and cervical cancer protection by non-medicated or Copper, IUDs remained inconclusive⁵⁶. LNG-IUS has numerous non-contraceptive benefits and various studies support the benefits in gynecological conditions. LNG-IUS is revealed to have a positive effect on hemoglobin, it was found that hemoglobin elevated after the device as inserted⁵⁷⁻⁶⁰. Frame-less LNG-IUS for contraception used by women showed decreased menstrual blood loss⁶¹. Several studies involving LNG-IUS using various design patterns reported beneficial results for menorrhagia, few studies showed a 74 to 97 % decrease in menstrual blood loss⁵⁶. In a study conducted by Lahteenmaki and his co-workers, it was found that bleeding days were lessened by 50%⁶².



Various randomized controlled trials and meta-analysis have shown that hysterectomy is essential as a conclusive treatment in those cases where women already had used LNG-IUS as well as conserving therapies^{63,64}. Another randomized controlled trial showed that hysterectomy may have some serious problems associated with it and no significant betterment in health in comparison to LNG-IUS, it also reported that LNG-IUS is more cost-effective than hysterectomy in the first year of insertion as well as in five years follow up⁶⁵. Two Randomized trials showed that LNG-IUS can be a feasible alternative to surgery, 80% and 64 % of women abandoned the plan for hysterectomy who were assigned LNG-IUS, and 9 and 14 % canceled hysterectomy respectively who were to receive conservative treatment^{62,66}. Due to Inherited, bleeding ailments menorrhagia may arise, as per a study, upon treatment with LNG-IUS menstrual blood loss decreased in patients with menorrhagia associated with Inherited bleeding ailments⁶⁷. Three Randomized trials showed that LNG-IUS insertion can lead to a reduced occurrence of fibroids. All other analysis which evaluated, the relation of LNG-IUS with fibroids showed that menstrual blood loss was reduced by 84-90%, and hemoglobin was elevated⁶⁸. Additionally, a case series suggest that endometrial hyperplasia may be cured with LNG-IUS^{69,70}. As per a case report, LNG-IUS and oral progestogens combined showed to reverse endometrial cancer⁷¹. A review of various case series and cohort studies reported that progestin therapy, is a secure and efficacious treatment of endometrium, this study sets up the credible role of LNG-IUS in the therapy of endometrial cancer⁷². Dysmenorrhea is a frequently reported disorder and 90% of younger women are impacted by it⁷³. Various studies reported that LNG-IUS is efficacious in managing dysmenorrhea and endometriosis linked pelvic pain⁷⁴⁻⁷⁶.

ADVANCEMENTS

Novel IUD Approaches:

To tackle the hemorrhage, and menstrual pain associated with Tcu380A copper IUDs, a novel approach is used that is the incorporation of indomethacin to copper IUDs of 5 unlike types developed. In China, indomethacin is an anti-inflammatory agent and it's been found that IUDs caused uterine bleeding was lowered by administering indomethacin via the oral route, also in a Morphometric study, it was found that, indomethacin releasing copper IUDs (IR-Cu-IUD) noticeably decreased uterine hemorrhage prompted by Cu-IUDs⁷⁷. Notably Chinese devices with indomethacin available are Medicated Gamma IUDs, Medicated Gamma cu380, and Medicated gamma cu200^{78,79}. However, in English literature only finite data regarding the efficiency of these Chinese medicated IUDs are available, but Chinese data illustrates the efficiency and advantages of these medicated IUDs over copper IUDs¹⁴. Cu200 is a distinctly shaped indomethacin medicated copper IUD having 200 mm² of copper surface area, identical to uterine shape. Cu200 is available in three sizes, the interior of the IUD frame is

made up of a stainless-steel wire tube lined by silicon rubber containing 18 mg indomethacin Medicated Gamma IUD has a 200-250 mm² copper surface area and it has gamma shaped stainless steel wire frame wrapped with copper wire. 25 mg of indomethacin is integrated into silicon elastomer beads present in the center of the device and at the ends of each arm⁸⁰. Another medicated IUDs is Gamma Cu-380 having stainless steel wireframe, with 380 mm² of copper wire wound up and 25 mg of indomethacin integrated. In a study conducted in which 600 women used medicated Gamma Cu-380 IUDs and no pregnancies over two years of use were found⁸¹. Medicated Cu-380 can only achieve Indomethacin controlled-release, but cupric ions cannot be controlled released by Medicated Gamma Cu-380 IUDs. Uncontrolled burst release of copper ions can cause endometrial injury and cell toxicity, to overcome this indomethacin/ copper/low-density polyethylene (IDM/Cu/LDPE) porous composite novel material has been developed, which controls IDM as well Cu ions release, by controlling its porosity release rate can be modified⁸². Another novel material is Chitosan/Alginate/Indomethacin layered on Cu/LDPE composite IUDs to overcome biocompatibility issues, and for better drug release. This novel medicated device could provide two types of mechanisms, from IDM/Cu film checked release of IDM and sustained delivery of copper ions, from Cu/LDPE composite⁸³.

Veracept is a novel copper device currently under development, it has a lesser dose of copper and thus declines hemorrhage, this device is made up of titanium alloy, nickel, and nitinol, so the frame is completely adaptable and thus comfortable. In a Randomized single-blinded comparative trial of the VeraCept device with copper T380S, it is reported that there is a lesser expulsion rate, and lesser pain during insertion and continuation rate is greater⁸⁴. Additionally, there are copper-containing nitinol IUDs, called Intrauterine ball (IUB) which takes up the spherical shape on the introduction to the uterus. Nitinol is an alloy having memory properties which makes it flexible. Seventeen copper sphere-shaped structures are accommodated with wire, having a spherical shape, makes this device more comfortable and decrease the risk of perforation, this device has a contemplated lifespan of 5 years⁸⁵.

Frameless Intrauterine devices:

If the size dimensions of the intrauterine device are more than the size of the uterus then it can cause discomfort, pain, and hemorrhage⁸⁶. So, a more adjustable and minor sized device will be suitable for nulliparous and young women. Frameless devices are available in two variants hormonal and non-hormonal devices. The uterine cavity is merely distorted by these devices because in place of a plastic T-frame they single suture core of propylene⁸². Gynefix is the copper frameless device, having a copper surface area of 330 mm²⁸⁷. In comparison to Tcu380A IUDs, the Gynefix frameless IUDs are highly efficacious as per a study. Hormonal Intrauterine device is Fibroplant



LNG-IUS having 5 years of duration of use over Gynefix fibroblast has an added convenience because of more efficacious contraceptives⁸⁸. This device has similarities to that of framed LNG-IUS in case of a decline in menstrual bleeding by 80% for patients of amenorrhea after two years⁸⁹.

Contraceptive Implants:

Unintentional pregnancy issues in any area cannot be fixed readily or rapidly, and the overwhelming majority of unforeseen births are possibly attributable to unavailability or avoidance of birth control methods⁹⁰. The guarantees of contraceptive implants still haven't been achieved in full, despite the more than 3 decades of

advancement, development, and application in industrialized world family planning programs, the key explanation is the massive costs. The increased cost per unit of implants in contrast with other types of contraceptives prohibits extensive adoption in countries with low funding⁹¹. Contraceptive implants were primarily developed for long-term sustained release to prevent more or less concentration of steroids periods and to relieve consumers of occasional administration. More than a million women across all continents are using the first to enter the market, known as Norplant⁹². Table 1 represents the primary features of three available implants.

Table 1. Major Features of the 3 Available Contraceptive Implants

	JADELLE	IMPLANON	SINO-IMPLANT II
Company	Bayer HealthCare	Merck	Shanghai Dahua
No. of Rods	Two	One	Two
Active constituent along with quantity (mg)	Levonorgestrel (150)	Etonogestrel (68)	Levonorgestrel (150)
Duration of use	5 years	3 years	4 years
Insertion and removal time by experts	Insertion: 2 min Removal: 5 min	Insertion: 1 min Removal: 2–3 min	Insertion: 2 min Removal: 5 min
Price	\$8.50	\$16.50	\$8.00

Source: Modified from a table prepared by FHI 360, the RESPOND Project, and USAID.

For preventing pregnancy, LNG implants are reported, no other clinical application is known. The implants are developed in two separate versions; as capsules made of silicone tubing implants filled with LNG or as implants in rods with a physical mixture of silicone elastomer and LNG and is encased by thin-walled silicone tubing⁹³. Around 72 percent of unintentional pregnancies appeared in one study of 16 developing countries because of the unavailability of birth control measures⁹⁴. The implant of LNG was correlated with rapid repetitive pregnancy (RRP) prevention among youths. In a study, LNG implants occurred at substantial concentrations greater than that of depot medroxyprogesterone (DMPA) and oral contraceptive pills (OCPs) among youths⁹⁵. The long-term highly efficient contraceptive protection offered by LNG implants is obtained at the lowest hormonal dosage. LNG acts at different target organs involved in the process of reproduction⁹⁶. For many years, LNG implants release low hormone dose continuously. LNG exercises its contraceptive function by inducing modifications of the cervical mucus, ovulation inhibiting, and ovulatory dysfunction⁹⁷. Installation and removal risks correlate with non-insertion, deep insertion, nerve injury, and needle - stick harm⁹⁸.

There have been almost three decades since a federal body licensed contraceptive implants. Since then, many million women have been using implants. Implant consumers usually have the lowest pregnancy prevalence and the highest continuity incidence in any reversed form in

contraceptive in clinical and cohort trials, and national probability samples⁹⁹.

FUTURE PERSPECTIVE

The optimal purpose of research into contraceptives should be to enhance current methods, allow better use of them through improved consumer access and create new methods that will provide extra benefits to health to enhance enforcement and the ability to use them¹⁰⁰. By 2025, the consumer base for contraceptives will be more than 2 billion women. It's necessary to build versatile, long-term, remarkably effective, and consumer-friendly contraceptives to meet the individual requirements of this increasing population. Significant progress has been made in refining current approaches to contraception and creating numerous new strategies¹⁰¹. Research on male hormone contraceptive production has recently accelerated and many approaches have been developed in the late stages. Also, hormonal contraceptives, as do hormonal contraceptives for women, can have other health benefits for men. However, as is the case with women contraceptives, acceptability is likely to differ greatly across populations¹⁰². Nowadays most formulations are crafted reasonably quickly and rendered into oral drug delivery types. However, this design often poses several challenges such as patient adherence, design difficulty, and even cost device that can monitor the rate, dosage, and distribution against precise goals. Finally, a dosage type that has not fluctuated the plasma concentration of the drug due to



patient non-compliance must be established. Finally, this dilemma could be solved by the implant¹⁰³.

CONCLUSION

Contraceptive implants are highly effective throughout the globe. Several million women currently use implants. The substantial growth in IUD usage in the last 60 years is attributed to the modernization of this procedure, which is medically permissible and can be conveniently implanted into the uterus without cervical dilation, and the collection and dissemination by the Population Council of a large number of protection and effectiveness results. One of the key reasons for IUDs discontinuation is IUDs exclusion for bleeding-connected cases and also due to the adverse events related to IUDs and implants. Therefore, in-uterine contraception systems that reduce the occurrence of bleeding, removal, and conception should be established in the priorities for future study. In many nations around the globe, misconceptions and lack of knowledge about IUDs have restricted visibility and acceptability to use.

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