Section A -Research paper

Cervical Changes in Long Term User of IUCD

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Abstract:

Intrauterine device (IUD) use has been shown to reduce the risk of endometrial cancer, but little is known about its association with cervical cancer risk.

Keywords: Intrauterine device, cervical cancer, IUDs.

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Introduction:

Intrauterine devices (IUDs) are one of the most effective forms of contraception available today, with rates of failure similar to various forms of sterilization. The two types of IUDs that are presently used, including the copper-containing IUD and levonorgestrel-containing IUD, have similar rates of preventing pregnancy, with failure rates of 0.08% and 0.02%, respectively. This makes these devices more than 99% effective in preventing pregnancy **(1)**.

In the United States, there has been an increased use of long-acting reversible contraception (LARC) since 1995. This use has continued to increase from year to year, with 14% of women who use contraception choosing to use a form of LARC. There has also been a decrease in the number of unplanned pregnancies with the increased use of LARC. Additionally, there are many benefits of IUDs, including efficacy, ease of use, reversible nature, and patient satisfaction, especially with time commitment for long-term use and cost **(2)**.

All IUDs currently available in the United States are T-shaped, with the top of the T resting across the top of the endometrial cavity. IUDs are between 28 mm to 32 mm wide and 30 mm to 36 mm long. Uterine width traditionally has been assumed to be adequate in all patients; however, recent ultrasound studies have indicated that cavity

width in nulliparous women may be narrower than device width. Therefore, it is important to consider the available IUD options available. The smallest IUDs measure 28 mm wide and 30 mm long and are best suited for nulliparous and young women **(3)**.

The precise mechanism of action for IUDs remains unclear and is complex. All types of IUDs cause endometrial changes that are spermicidal, inhibiting sperm migration through the endometrium. In the IUDs, there is decidualization and atrophy of the endometrial glands, which leads to reduced sperm capacitation and survival but might also inhibit implantation of the fertilized ovum. IUDs also cause thickening of the cervical mucus, which inhibits the passage of sperm through the cervix. In general, IUDs do not effectively suppress ovulation. IUDs do not disrupt pregnancy and are not abortifacient (**4).**

Infections with high-risk HPV types, especially persistent infections, are necessary for the development of high-grade precancerous cervical lesions. These lesions are known as CIN grades 2 and 3, and adenocarcinoma in situ (AIS). If undetected and untreated, precancerous lesions can progress to cervical cancer **(5)**.

Intrauterine devices (IUDs) are associated with inflammation in the genital tract, and they may alter the natural history of HPV infections, including development of cervical cancer. It was found a decreased risk of cervical cancer associated with IUD use **(6**) while other studies have shown no association between IUD use and cervical cancer **(7)**. These studies were limited by use of an ever/never classification of IUD exposure and therefore little is known about more proximal relationships between IUD use and development of precancerous cervical lesions and cervical cancer. Only one of these studies reported the types of IUDs used, and given the time frame, they likely primarily included inert and copper-containing devices **(8)**.

Understanding exposures that increase risk of progression of hrHPV infection to cervical dysplasia and/or cancer can help target outreach activities to increase coverage of vaccination and/or screening**(9)**.

One exposure hypothesized to increase the risk of progression of hrHPV infection to cervical dysplasia/cancer is combined oral contraceptive (COC) use. The International Agency for Research on Cancer (IARC) has classified COCs as a cause of cervical cancer **(10)**.

A hormone-containing intrauterine device (HIUD) is widely used as a preferred contraceptive method and in treatment of irregular bleeding. In Denmark, the annual number of HIUD sold increased from 15,000 in 2005 to 62,000 in 2017 (Sundhedsdatastyrelsen). Evidence is sparse and diverse on HPV infections and precancerous cervical lesions in women using HIUD compared with women using other contraceptive methods **(11)**. Two meta-analyses including mainly case–control studies of patients with cervical cancer found IUD use, HIUD and CIUD combined, as compared with non-IUD use, to be associated with a lower risk of cervical cancer **(12).** As non-IUD users may include both OC users

and women not using contraceptives, it is difficult to say whether these findings indicate a true protective effect of IUD use.

In a US case–control study, IUD use compared with non-IUD use did not affect the risk of CIN3+; odds ratio (OR) 0.98 and only marginally for CIN2+; OR 1.09, and this pattern was the same when the comparison was made with users of other hormonal contraceptives. Compared with the non-IUD users, the OR for CIN3+ for HIUD was 1.05 and for CIUD it was 0.81, with the slight excess risk for CIN2+ in all IUD-users coming from the HIUD group; OR 1.18 **(8).** Independent of comparison group, this study indicated limited impact of IUD use on the risk of high-grade cervical lesions.

In a large cohort study from the Netherlands, IUD and OC users had an excess risk for CIN3+; RR 1.51 and RR 2.77, respectively, compared with women using neither IUD nor OC. OC users had an increased risk of CIN3+ compared with IUD users; RR 1.83. Results for cervical cancer pointed in the same direction but were statistically significantly increased in OC users only **(13).**

It was found that 1 year after insertion, HIUD-users had more persistent HPV infections and more new HPV infections than CIUD users (n = 150) **(14)**.

It was reported that the HPV infection rate was the same in IUD users as in users of other contraceptive methods, and HIUD use did not affect risk of positive cervical cytology and high-grade lesions. In a study concerning effect of HIUD use on properties of the mucosal immunity of the upper reproductive tract, both inflammatory and immunosuppressive changes were observed although it was uncertain how these changes would affect the risk of viral infections **(7)**.

The effect of IUD by type, particularly IUDs that release the hormone levonorgestrel (LNG), on development of cervical cancer is not well understood. There is some evidence to suggest a possible association between hormonal contraceptive exposure and increased risk of cervical cancer, particularly with long durations of combined hormonal contraceptive use (≥10 years) or injectable contraceptive use (≥5 years). This perceived association could be due to selection bias since hormonal contraception implies sexual activity and HPV is a sexually transmitted infection **(15)**.

Women of reproductive age choose between a number of contraceptives during a time in life when HPV infections are very common. Understanding the effect of contraceptives on the natural history of HPV infection, and subsequent development of precancerous lesions of the cervix and cervical cancer, may provide information that is valuable to women in contraceptive decision-making. The question remains whether IUDs are associated with decreased risk of cervical cancer, and if so, the effects of IUDs on the chain of events from HPV infection to cervical cancer. The goal of this study was to evaluate the association between recent IUD use (by type) and high-grade precancerous cervical lesions (CIN2, CIN3 and AIS) and cervical cancer (collectively known as CIN2+ or CIN3+)**(8)**.

A variable association between IUD use and cervical pre-cancer and cancer was reported. When stratified by IUD type, LNG-IUD use was associated with CIN2+ but not CIN3+. Copper-IUD use was not associated with pre-cancer or cancer. It is unclear whether the observed association between IUD use and CIN2+ is causal or whether residual unmeasured confounders account for the observed association (i.e., differential sexual activity, and therefore differential risk for HPV, between IUD users compared and non-users) **(16)**.

Sexually transmitted infection (STI) testing was adjusted as a marker of new sexual partners and HPV exposure, but this is a not a validated marker of exposure. The Kaiser Permanente Medical Care Program of Northern California (KPNC) members represent a well-screened population overall, so it is unlikely that there are significant differences in screening, treatment, or diagnosis for women with and without IUD use **(17)**.

When only non-IUD contraceptive users were compared to IUD users, excluding non-contraceptive users, the association between CIN2+ and IUD use was no longer seen which supports the possibility of residual confounding. The association was found between hormone-containing LNG-IUDs and CIN2+ continues to raise the question of whether there may be a small deleterious effect of contraceptive hormones on development of cervical pre-cancer. There has been an association observed between hormonal contraceptives and both CIN3 and cervical cancer but whether these observations are causal has been questioned **(18)**.

Whether contraceptive hormones, either ethinyl estradiol or progestins, affect progression to CIN among women with persistent HPV infection is unknown and has been highlighted as a priority area for research **(19)**. The effect of progestin-only contraceptives, and the differences between local and systemic delivery of progestin hormones, on risk of cervical cancer is poorly understood. While the direct effect of LNG on cervical cancer has not been well studied, a small association has been seen between cervical cancer and injectable contraceptive use (5 years or more), although this conclusion is based on limited published data **(20)**.

In addition, it was reported that the new IUD users who had HPV infections found that copper IUD users were more likely to clear HPV infections than LNG-IUD users. It was suggested that the anti-inflammatory properties of LNG may inhibit HPV clearance **(14)**. Some progestins have effects on immune parameters that alter susceptibility to viral infections including effects on innate anti-viral factors such as human B-defensins, and on pro-inflammatory chemokines and cytokines**(21)**.

Since HPV clearance depends on cellular immunity, it is possible that progestin exposure could increase or decrease HPV clearance. It was found that the risk of CIN2 was elevated among recent LNG-IUD users but the risk of CIN3 was not. As CIN2 is in the low-grade spectrum, this suggests a perturbation on the HPV infection/regression

end of the spectrum, not on the carcinogenic end of the spectrum, which is further reassurance that IUDs are safe for women with HPV-related disease. While power may be limited when looking at associations between IUD use and CIN2 or CIN3 alone, the magnitude of the measure of association is still meaningful and the reasonably narrow confidence intervals would suggest a moderate degree of precision **(11)**.

It was demonstrated a statistically significant decrease in cervical cancer associated with IUD use; women who reported ever using an IUD had a decreased likelihood of being diagnosed with cervical cancer compared with never users. Previous research included adjusted for self-reported number of lifetime cytology (Pap) tests. Given the timing and location of the studies included, the IUDs used were most likely almost exclusively copper-IUDs **(12)**.

There was a trend towards decreased risk of CIN2+ among copper-IUD users. Therefore, it is possible that there is a modest protective effect of copper-IUDs, and this is an area for future research. It was showed that there was no association between ever using an IUD and CIN3+, but there was a trend towards a protective effect of IUD use. In a nested case-control study of HPV sero-positive women, IUD use was associated with a statistically significant decrease in the risk of CIN3+ **(22)**.

In addition to its contraceptive benefits, IUD can protect against precancerous lesions of the cervix in HPV infected women **(23)**. The association between IUD (by duration of use) and cervical cancer was evaluated, it was found that > 5 years of IUD use was protective against cervical cancer while < 5 years was not while no association between cancer and > 5 years IUD use was also reported **(23)**. It was observed that women who had any recent IUD use because one proposed mechanism for the protective effect of IUDs on cervical cancer is the hypothesis that the transformation zone is manipulated during IUD placement eliciting an immune response that promotes clearance of HPV and pre-cancerous lesions **(24)**.

If the observed association between the LNG-IUD and CIN2+ is causal, the true attributable risk is likely small. Furthermore, LNG-IUD use was associated with CIN2, a transient infection, but not CIN3, a high-grade pre-cancer. The lack of association between LNG-IUDs and CIN3+ suggests that there may not be a clinically meaningful harmful effect. The lack of association between IUD use and CIN2 when compared to other contraceptive use only suggests residual confounding or bias related to sexual behavior may be present. Given the clear benefits of highly effective long-acting contraception, these findings should not be used to limit the use of all types of IUDs among women with cervical dysplasia or at risk for cervical dysplasia **(8)**.

It was reported that in women with normal cytology at the time of initiating contraceptive use, it was found that HIUD and CIUD users over the next 5 years had a lower risk of CIN2 and CIN3+ than OC users. Users of HIUD were more likely to have a normal histology or low grade CIN1 diagnosis than women using either CIUD or

OC. This was in particular seen in women with only 1–2 years of HIUD use and may possibly be explained by diagnostic follow-up of irregular bleeding following the HIUD insertion. Among women followed up with cytology only, HIUD and CIUD users had lower risk of abnormalities than OC users **(11)**.

It was reported that patients with cervical cancer found IUD use, HIUD and CIUD combined, as compared with non-IUD use, to be associated with a lower risk of cervical cancer. As non-IUD users may include both OC users and women not using contraceptives, it is difficult to say whether these findings indicate a true protective effect of IUD use **(12)**.

In summary, the estimated risks of CIN3+ associated with IUD use varied considerably depending on the comparison group included in the analysis. It was indicated that the risk of high-grade precancerous cervical lesions was higher in women requesting contraceptives than in women not requesting contraceptives or in women using OC; probably reflecting differences in sexual behavior and lifestyle. To avoid this selection bias, an internal comparison between users of various contraceptives might, therefore, be more reasonable. IUD users were consistently found to have a lower risk of CIN3+ than OC users, and data indicated that this was true for both HIUD and CIUD users **(11)**.

Women requesting contraception are at higher risk of acquiring HPV infections and of developing precancerous cervical lesions than women who do not request contraception. For women with normal cytology at the time of insertion, A 37–42% lower risk of severe precancerous cervical lesions was observed in IUD users than in OC users that could derive from a risk associated with OC use and/or a protection associated with IUD use. In the case of protection associated with IUD use, a possible explanation could be that the IUD generates an inflammatory response in the endocervical canal, which could lower the risk of HPV infection **(25)**.

CIUD users tended to have a lower risk of high-grade cervical lesions than HIUD users, which could possibly be explained by differences in their mechanism of action. CIUDs release copper ions in the uterine cavity causing the development of chronic inflammation, whereas HIUDs decrease prostaglandin levels causing suppressed local immunity, and may lead to a higher risk of persistent HPV infections**(8)**.

For women with high-grade precancerous cervical lesions at the time of recruitment, it was found the same progression rate for HIUD users as for CIUD and OC users. For women with low-grade lesions, normal histology and abnormal cytology at recruitment, HIUD users had lower progression rates than the two other user groups **(11)**. For persistence and regression of lesions at time of recruitment, no difference was observed between the three groups. When exploring the development during the first 5 years after insertion, previous findings suggested that the HIUD is an acceptable contraceptive method both for women with normal cytology at the time of

insertion and for women with precancerous cervical lesions at the time of insertion**(11)**.

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