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Dry 'intrauterine swimming pool' for the sperm – a potential new mechanism of action of levonorgestrel-releasing intrauterine system (LNG-IUS, Mirena) as a contraceptive

Abstract

The research Question: What is the predominant mechanism of action of levonorgestrel-releasing intrauterine system (LNG-IUS) as a contraceptive?

Study Design: Review of the literature has been undertaken on the mechanisms of action of LNG-IUS as a contraceptive, endometrial changes following the use of LNG-IUS and process of natural conception, especially sperm transport through the female reproductive tract.

Findings: In the literature, the mechanisms of action of LNG-IUS as a contraceptive include impairment of sperm transport through the cervix due to thick cervical mucus and through the uterus due to inflammatory changes in the endometrium affecting sperm transport and function, and possibly fertilisation and implantation are impaired. The evidence from the literature shows that following long-term use of LNG-IUS the changes in the endometrium is predominantly atrophy and decidualisation not inflammation, the latter being a feature during the initial phase after its insertion. As endometrial atrophy is the predominant feature of long-term LNG-IUS use, impairment of the sperm transport through the uterus due to inadequate volume of endometrial fluid might play a major role in the mechanism of action for its contraceptive effect.

Implications: Further research in to the area would be useful, not only to improve insight in to the mechanism of action of contraceptives but to explore areas in the process of natural conception and causes of infertility, especially in relation to the endometrium and intrauterine sperm transport. Contraceptive IUS, releasing non-hormonal drug(s), which would reduce the endometrial secretions without causing hormonal side-effects might become another contraceptive option in the future.

Keywords: LNG-IUS, contraceptive mechanism of action, intrauterine sperm transport, endometrial atrophy, endometrial fluid

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Introduction

Intrauterine devices (IUDs) are the most widely used, safe, effective and low maintenance long-term reversible contraceptive method. Worldwide, they are very popular, second only to female sterilisation (13.6% vs 20.5%).[1] They are used by over 150 million women worldwide for contraception (over 100 million women in China only). In women using contraceptives, the prevalence of IUD use include 15%, 8% and 2% in developing countries, developed countries and the United States respectively.[2] The levonorgestrel-releasing intrauterine system (LNG-IUS) has gained popularity as a contraceptive and for its non-contraceptive uses since it became available in Europe in 1990 and the United States in 2000. It is marketed under the name Mirena® (Bayer Schering Pharma, Berlin, Germany). It is highly effective contraceptive for up to five years (pregnancy rate <2 per 100 insertions). It is a T-shaped device composed of a polymer cylinder containing 52 mg of LNG covered by a rate-controlling membrane which serves to regulate the rate of hormonal release. The levonorgestrel (LNG) release is 20 µg every 24 hours that decreases to 11 µg every 24 hours by the end of five years, with an average release rate of 14 µg per day over the life of the IUS.[1,3] The estimated number of LNG-IUS users worldwide in year 2004 was more than 4 million in approximately 100 countries.[4]

The concept of the contraceptive effect of a foreign body in the uterus (IUDs) has been known for over 2000 years, still its mechanism of action is not entirely clear.[5] Research in to this area has been constrained due to lack of ideal animal models, in addition to ethical and religious reasons. These may explain why research into the contraceptive mechanisms of IUDs has been sparse since the late 80's as the researchers and agencies involved in the development or delivery of contraception have left the mechanism of action issue unresolved.[6] The mechanism of action of the LNG-IUS is similar to that of LNG implants or LNG-containing mini-pills, but at a much lower peak serum levels than other progestogen-containing contraceptives e.g. 0.1–0.4 ng/ml vs 1.7–15.2 ng/ml with combined and progestogen-only oral contraceptives respectively, and 5.4 ng/ml for combined vaginal preparations.[1,3]

It is interesting that despite available evidence that endometrial atrophy is the predominant feature following long-term use of LNG-IUS rather than inflammatory changes in the endometrium, which is a short-term initial feature, this area has not been explored or explained in detail in the literature on contraceptive mechanism of action of LNG-IUS, especially in relation to the intrauterine sperm transport. The explanations in relation to the effects of the endometrial changes on sperm transport and function have primarily been centered on

the inflammatory changes. Therefore, a literature search has been performed to find the potential effect of endometrial atrophy on the intrauterine sperm transport and the results included here.

Materials and methods

The literature on the mechanisms of action of LNG-IUS as a contraceptive, endometrial changes following the use of LNG-IUS and process of natural conception especially sperm transport through the female reproductive tract were searched online and reviewed.

Statistical analyses: Not required.

Ethical approval: Not required as it did not involve experiments on human subjects or use of personal data.

Results

Mechanisms of action of LNG-IUS as a contraceptive – the literature

To act as a contraceptive LNG-IUS needs to interfere with at least one or more of the natural processes of conception e.g. ovulation, sperm transport and function, oocyte quality and fertilisation, and implantation.[1,7]

Ovulation: There is no strong evidence that disruption of ovulation contributes to its contraceptive effect.[8–13]

Sperm transport and function: Sperm move from the cervix to the Fallopian tube and peritoneal cavity within about an hour of deposition in the vagina. The sperm numbers in the ampulla of Fallopian tube have been found to be reduced in women with copper IUDs or LNG-IUS.[14,15] Copper ions are toxic to spermatozoa[16] and LNG alters the quality of cervical mucus, making it hostile to the sperm transport through the cervix.[17,18] In addition, LNG may affect sperm function[19] that might affect the fertilising ability of the high quality sperm that reach the tube. The fact that pregnancy do occur, although rarely, in presence of LNG-IUS provides evidence that some sperm still remain capable of fertilising the oocyte.[1,7]

Oocyte quality and fertilisation: The studies undertaken to find whether fertilisation occurs in presence of IUDs or LNG-IUS concluded that although fertilisation does occur in some women, development of the embryo may be impaired.[1,7] This was more likely to happen with copper IUDs than LNG-IUS or inert IUDs.[20]

Implantation of the embryo: Implantation of the embryo in the uterus usually occurs 6-7 days after fertilisation. In women with copper IUDs, inflammatory cells enter the endometrium and prostaglandin production is excessive.[21] In women with the LNG-IUS, the endometrium is abnormally thin and contains areas of superficial fragile vessels suggesting that the uterus would be hostile to implantation.[22] Expression of genes associated with implantation, e.g. the genes for glycodelin and leucocyte inhibition factor, is also altered in women with copper IUDs.[23] The fact that copper IUDs are highly effective emergency contraceptive and is associated with increased ratio of ectopic to intrauterine pregnancies, suggests that the copper IUDs can act after fertilisation and prevent implantation.[7,24,25] In contrast, LNG-IUS is not effective as emergency contraception.[1]

In summary, the contraceptive action of LNG-IUS may be the result of its actions in multiple areas of the natural process of conception. Potentially, the movement of sperm through the cervix is impaired due to thickening of the mucus. It also interferes with sperm function, and transport within the uterus and tubes. Whether fertilisation of the oocyte is impaired by these compromised sperm is not clear. It might prevent and disrupt implantation. The extent to which this interference contributes to its contraceptive action is unknown. The data are scanty and the political consequences of resolving this issue interfere with comprehensive research.[1,7]

Sperm transport – the literature

Human sperm, within few minutes of being deposited in the vagina, start leaving the seminal pool and swim into the cervical canal.[26] The extent of hydration of the cervical mucus is correlated with penetrability to sperm.[27] Cervical mucus may help with sperm selection by presenting a greater barrier to abnormal sperm that cannot swim properly or that present a poor hydrodynamic profile than it does to morphologically normal, vigorously motile sperm.[28–31]

Intrauterine sperm transport

The swimming speed of sperm in aqueous medium is about 5 mm/min.[32] Although the time taken by the sperm to traverse the uterine cavity is variable and difficult to assess, sperm have been recovered from the Fallopian tube within 5-10 minutes of insemination.[33–35] Transport of sperm through the uterus might be enhanced by pro-ovarian myometrial contractions that might be stimulated by seminal components.[36–38] Myometrial contractions may draw sperm and watery midcycle mucus from the cervix into the uterus.[39] It may assist sperm movement through the uterine cavity that contains only about 100µl of fluid in midcycle.[40] Sexual intercourse induces a leukocytic infiltration (primarily neutrophils) of the uterine cavity, which reaches a peak several hours after mating in mice[41] that phogocytose primarily damaged uterine sperm in animals.[41,42] Normal sperm, however, may also be phagocytosed, particularly in vaginal inseminators like humans, because the sperm would lose most of the immune protection afforded by seminal plasma constituents.[43,44] *Initially, when sperm enter the uterus, they outnumber the leukocytes, but as time passes, the leukocytes begin to outnumber sperm. Rapid transport of sperm through the uterus in to the Fallopian tube before significant numbers of leukocytes arrive may be required to enhance fertilisation.[45] Progress of sperm in to the Fallopian tube may also be impaired by viscous mucus at the narrow lumen of the uterotubal junction.[46]

*Video: Sperm attacked by woman's immune system - Inside the Human Body: Creation - BBC One. Its worth watching. https://www.youtube.com/watch?v=MoAUfnKcA3I

Discussion

The natural process of conception following deposition of semen in the vagina involves the sperm swimming through the cervix, the uterine cavity and utero-tubal junction in to the Fallopian tube to fertilise the ovum, and the fertilised ovum/embryo moving in to the uterus and getting implanted there successfully. The inert IUD, as a foreign body, makes the intra-uterine environment hostile for the sperm and embryo through an inflammatory response.[7,43] The copper IUD makes the intra-uterine environment hostile for the sperm and embryo through an inflammatory response as a foreign body and releases copper that is toxic to the sperm and embryo, the latter being the predominant mechanism of action.[1,3,7,48] In addition, copper IUDs raise the copper concentration in the cervical mucus substantially[49] that has been shown to inhibit sperm motility.[50]

The LNG-IUS, as a foreign body, makes the intra-uterine environment hostile for the sperm and embryo through an inflammatory response, and in addition releases LNG that leads to endometrial atrophy and makes the cervical mucus thicker.[3] It may

make the mucus at the uterotubal junction thicker, the endosalpinx atrophic, and reduce/modify the myometrial and Fallopian tube muscle contractions.[51,52] All of these may impair sperm transport from the vagina to the Fallopian tube, sperm function, fertilisation and implantation.

The mechanisms of action of LNG-IUS as a contraceptive in the literature include

i. Impairment of sperm transport through the uterus and sperm function due to hostile intra-uterine environment (e.g. leucocyte infiltration etc) created through an inflammatory response as a foreign body. This is the usual mechanism reported by which LNG-IUS impairs sperm transport through the uterus and sperm function. How the other endometrial changes (e.g. atrophy) might affect sperm transport through the uterus and sperm function has not been explained in greater detail.

ii. Impairment of sperm transport through the cervix due to thick cervical mucus.

iii. Possible impairment of fertilisation.

iv. Possible impairment of implantation of the embryo in the uterus, in case the sperm manages to fertilise the ovum, due to hostile intra-uterine environment created through an inflammatory response as a foreign body and endometrial changes (atrophy etc).[1,3,7]

What is the likely predominant mechanism of action of LNG-IUS as a contraceptive?

Copper IUD vs LNG-IUS: The toxic effect of copper on the sperm and embryo affecting sperm transport through the cervix and uterus, and implantation of the embryo is the primary mechanism of action of the copper IUDs besides the creation of a hostile intra-uterine environment for the sperm and embryo due to inflammatory response as a foreign body. The former is not applicable to LNG-IUS as there is no evidence that LNG is as toxic as copper to the sperm and embryo.[1,3] Regarding the inflammatory response, endometrial expression of pro-inflammatory cytokines has been shown to be significantly lower after the use of LNG-IUS when compared with their expression after the use of a copper IUDs.[53]

Inert IUD vs LNG-IUS: The primary mechanism of action of the inert IUDs like the Lippes loop is the creation of a hostile intra-uterine environment for the sperm and embryo, through inflammatory response, potentially affecting sperm transport through the uterus and implantation of the embryo.[7,47] The LNG-IUS would have a similar effect,[47] likely to be of a lower magnitude as the volume of LNG-IUS is smaller than the Lippes loop. LNG-IUS, however, has significantly greater contraceptive effect compared with the inert IUDs. Therefore, it is unlikely to be the predominant mechanism of action of LNG-IUS. It is likely that there is another predominant mechanism of action. This is supported by findings in the literature that in the first months following insertion of the LNG-IUS, the endometrium exhibits many characteristics consistent with an inflammatory response, including leukocyte infiltrate, elevated cytokine and prostaglandin production, and expression of matrix metalloproteasess. All the markers of inflammation in the endometrium are initially high, however, these diminish gradually by 6 months post-insertion with long term local LNG delivery.[53] As LNG-IUS is effective for 5 years,[3] it is unlikely that inflammatory response of the endometrium is the primary/predominant mechanism of action of LNG-IUS as a contraceptive.

Progestogen-only pills (POP) vs LNG-IUS: The primary mechanism of action of the POP is by thickening of the cervical mucus affecting sperm transport through the cervix. The concentration of LNG in the blood in a woman with LNG-IUS is significantly less than that of a woman taking POP despite LNG-IUS having a greater contraceptive effect.[3] The LNG concentrations in the cervix are expected to be substantially lower than that in the endometrium. In a study of long-term LNG-IUS users, 69% of the ovulatory cycles had cervical mucus favourable for sperm transport.[10] Therefore, it is unlikely that thickening of the cervical mucus is the predominant mechanism of action of the LNG-IUS. It is one of the mechanisms of action, but there is likely to be another predominant mechanism of action.

LNG-IUS: Dry intrauterine 'swimming pool' for the sperm: As LNG-IUS is an intrauterine system its predominant mechanism of action is likely to be intrauterine. The endometrial concentrations of LNG are high, ranging from 470 to 1500ng/g of tissue weight and sustained over the 5 years of use. The LNG concentrations in myometrial and Fallopian tube tissues are much lower at 1.8–2.4ng/g.[1] The high local LNG concentrations achieve atrophy of the endometrial glands as has been documented by histological examinations and this effect has been greatly credited for the improvement in heavy menstrual bleeding for which LNG-IUS has been used successfully for years.[22,54,55] The morphological changes in presence of LNG-IUS include extensive decidualisation of the stroma, atrophic glandular and surface epithelium, and alterations in the vasculature. Secretory activity within epithelial glands ceases and the proliferative activity of the endometrium is inhibited. This results in the general thinning of the functional layer of the endometrium. These morphological changes occur rapidly, with loss of cyclical activity apparent after 1 month of intrauterine delivery. During the initial months following insertion of the LNG-IUS, areas of endometrium showing secretory appearance are found within the decidualised stroma,[53] however, with prolonged use the morphological changes become much more uniformly distributed throughout the endometrium.[56] Atrophy of the endometrial glands would lead to reduction in endometrial secretions and the volume of fluid in the endometrial cavity.[53,57] The sperm can move by swimming only[58,59] and they require a 'swimming pool' to swim. To swim they require a minimum depth of fluid in the 'swimming pool' as well. If the depth of fluid in the endometrial cavity is lower than the minimum required by the sperm to swim that would hinder their movement towards the Fallopian tube.[40,45] The potential change in the viscosity of the endometrial fluid could affect the sperm motility as well.[27,58,59] The longer the sperm stay in the uterine cavity they are more likely to be phagocytosed by the leucocytes that happens naturally following unprotected sexual intercourse.[43,44] The picture would be similar to fishes trying to swim in very shallow water inadequate for swimming and being picked up by birds. Even without phagocytosis, if the sperm cannot move towards the Fallopian tube, they would not be able to fertilise the ovum. As endometrial atrophy is the predominant feature of long-term LNG-IUS use, impairment of the sperm transport through the uterus due to inadequate volume of endometrial fluid might be the predominant mechanism of action for its contraceptive effect. The thickening of the cervical mucus acts as a first line of defense reducing the number of sperm that could enter the uterine cavity. The sperm, usually the best ones, which manage to bypass the cervical mucus[45] then might encounter the dryer swimming pool in the uterine cavity that would make swimming difficult thereby affecting sperm transport through the uterus and possibly sperm function. In the unlikely event when fertilisation occurs, the embryo would be less likely to have a successful implantation in the atrophic and relatively dry endometrium.[57,60]

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Conclusion

The usual mechanisms of action for the contraceptive effect of LNG-IUS stated in the literature include thickening of the cervical mucus affecting sperm transport through the cervix, and inflammatory changes in the endometrium affecting sperm transport through the uterus and sperm function, possible impairment of fertilisation and possible impairment of implantation of the embryo in the uterus. Drying of the 'swimming pool' in the endometrial cavity due to reduction in the endometrial secretions as a consequence of atrophy of the endometrial glands, however, might be the primary/predominant mechanism of action. In the literature, this potential mechanism has not been explored/explained in detail. Further research in to the area would be useful, not only to improve insight in to the mechanism of action of contraceptives but to explore areas in the process of natural conception and causes of infertility, especially in relation to the endometrium and intrauterine sperm transport. If this potential mechanism of action of LNG-IUS as contraceptive could be established, it might pave the path towards developing contraceptive IUS releasing non-hormonal drug(s) that would reduce endometrial secretions without causing hormonal side-effects.

Author's role

Sudipta Paul is the sole Author who contributed to the study including participation in study design, execution, analysis, manuscript drafting and critical discussion.

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Conflicts of interest

The authors declare there is no conflict of interests.

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