Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/a6910h32

CONTRACEPTIVES RELATED TO UTERINE CANCER

Muhammad Haris Baig[1*], Muhammad Hashim[1], Muhammad Huzaifa[2], Dr Fazal Hanan[3], Muhammad Aafaq Bashir[1], Izza Rafique[4], Muhammad Qamar[1], Muhammad Junaid Afzal[2], Dr Farah Abid[5], Muhammad Atif[2]

[1*]College of Allied Health Professionals, Government College University, Faisalabad, Pakistan.
[2]Cholistan University of Veterinary and Animal Sciences Bahawalpur
[3]Saidu Medical College Swat
[4]Department of Biochemistry University of Agriculture Faisalabad
[5]University of South Asia

***Corresponding Author:** Muhammad Haris Baig
*College of Allied Health Professionals, Government College University Faisalabad. Pakistan
Tel: +923177019577, Email: mhb8677@gmail.com

Abstract:
Background: The uterine lining, or endometrium, serves as where uterine cancer, often referred to as cancer of the endometrium, begins. It is the type of uterine cancer which damage women's reproductive systems the most frequently.
Methods: Application of different hormonal and non-hormonal contraceptives on uterine cancer.
Results: Obesity, diabetes, hormonal imbalances (such as high estrogen), and a family history of the illness are risk factors for uterine cancer.
Conclusions: It has been showed that combined oral contraceptives, which contain both progestin and estro-gen, lower the risk of uterine cancer by controlling hormone levels , which reduces the endometrium's exposure to estrogen.

Keywords: Uterine Cancer, Contraceptives, Hormonal IUDs, non-Hormonal IUDs

1. INTRODUCTION

Uterine cancer belongs to un controlled and unwanted growth of cells in uterine membranes. Contraceptives and uterine cancer actually interact with one another, in this era prevention of unwanted pregnancy and uterine cancer has paramount importance. Contraceptives are classified as hormonal or non-hormonal, two major classifications which actively relate with endometrium cancer. Endometrial cancer which begins from the internal lining of the uterus. It is associated with hormonal changes as well as non-hormonal changes i.e. excess of Estrogen in circulation. Womb cancer, endometrial cancer. Cancer of uterus is a commonly considered as uterine cancer. Internal lining of womb or uterus is called endometrium [1]

UTERINE CANCER EPIDEMIOLOGICAL STUDIES

Uterine cancer is the fourth most common serious condition among women in US. Womb cancer is most leading diagnosed Cancer in world .Uterine cancer strongly co relate with age about 75% of diagnosis appears in those women's who have 55 years above age. Until millions of the death of uterine cancer are diagnosed in US as well as Asians. According to estimation, [2] almost 46470

women in America was diagnosed with this disease in 2011 with 18.5% mortality rate and causing 10170 deaths. It is estimated that in 2011 any woman that born in US has a lifetime risk of one in 13 of upcoming uterine cancer.[3]
In 2015 in US, mortality rate due to train cancel was 18.5% and it is estimated that 54000 cases were reported in USA and the causing deaths was 10000. Ovarian cancer is a too much fatal than uterine cancer. In 2014, 21290 ovarian cancer patients were diagnosed and there were 14180 deaths with 66.6% mortality rate
In 2023 66200 new cases of uterine cancer are diagnosed until from which 1330 women die from endometrium cancer.[3] From 2017 to 2019, 14% of young women ranges from 15 to 49 years aged used oral Hormonal contraceptives. And 16% women did same oral activity in 2019 according to United Nations.[4, 5]

What is uterine cancer?
The cancer that occurs impact the female reproductive tract is uterine cancer, as endometrial cancer. A benign tumor can enlarge but often does not invade nearby organs. The following uterine disorders are not cancerous:

Endometriosis: a disorder where the tissue of the endometrium, that usually borders the outside of the female reproductive system, is found outside the uterus. Endometrial hyperplasia is a condition when the uterine lining has an increased density of cells and glandular arrangements. Endometrial hyperplasia can comprise common or atypical cells, as well as simple or intricate glandular structures. When endometrial hyperplasia has aberrant cells along with complicated organs, the chance for creating malignant growth in the uterine covering is increased. There are two main categories of cancerous uterine growth: Adenocarcinoma and endometriosis carcinoma. Most uterine tumors are of adenocarcinoma kind. It develops from endometrial or uterine lining cells. Typically, this condition is referred to as endometrial malignant development. Endometriosis carcinoma is the name given to one subtype of normal endometrial cancer. A specific type of uterine cancerous development occurs in the tissues that support the uterine organs, the outer layer inside uterus, or the myometrium.[6]

Differentiate between uterine and endometrial cancer
Here is the distinction between the two to make it clear:

Table. 1 Description of Various sorts of cancer

Uterine Cancer	Endometrial cancer
Any malignancy that arises in the uterus, the pear-shaped organ in a woman's pelvis where a fertilized egg implants and a pregnancy develops, is referred to as uterine cancer, which is a broad word.	The endometrium, or inside wall that covers the uterus, is the primary site of endometrial cancer development. With more than 90% of cases, it is the most prevalent kind of uterine cancer. Endometrial cancer typically originates from the cells that line the inside of the uterus and is often linked to hormonal alterations, notably elevated estrogen levels. Obesity, hormone treatment, diabetes, and a few hereditary illnesses are all endometrial cancer risk factors.[7]

Is Uterine cancer same as endometrial cancer?
However, the term "uterine cancer" is an all-encompassing term that refers to both uterine sarcoma and endometrial cancer, two different cancer forms.[7]

Risk factor:
Figure 1 is showing that about risk factors on base of age distributions of females are Excess body weight, Type 2 diabetes, Polycystic Ovarian Syndrome (PCOS),Gene changes (It's common for endometrial tumors to have broken PTEN, one of the favorable genes that regulates developing a tumor. Without certain tumor suppressor genes, such as the KRAS and TP53 genes, endometrial malignancy is more likely to recure after first therapy).

Figure 1. shown that females who use contraceptives are more prone to these mentioned abnormalities

There is another risk factor related to uterine cancer is Alterations in the body's hormone Balance i.e. Estrogen and progesterone are the two primary hormones that the ovaries produce. The endometrium changes as a consequence of changes in the hormone balance. The potential of developing cancer of the reproductive tract can rise in the presence of an illness or condition that raises the body's levels of progesterone but not estrogen. Examples include the polycystic obesity, diabetes, and irregular ovulation patterns. using estrogen-containing hormone treatment drugs but after menopause progesterone can be risk of Endometrium cancer. Demographic pattern among females is described in Figure 2 and table 1.

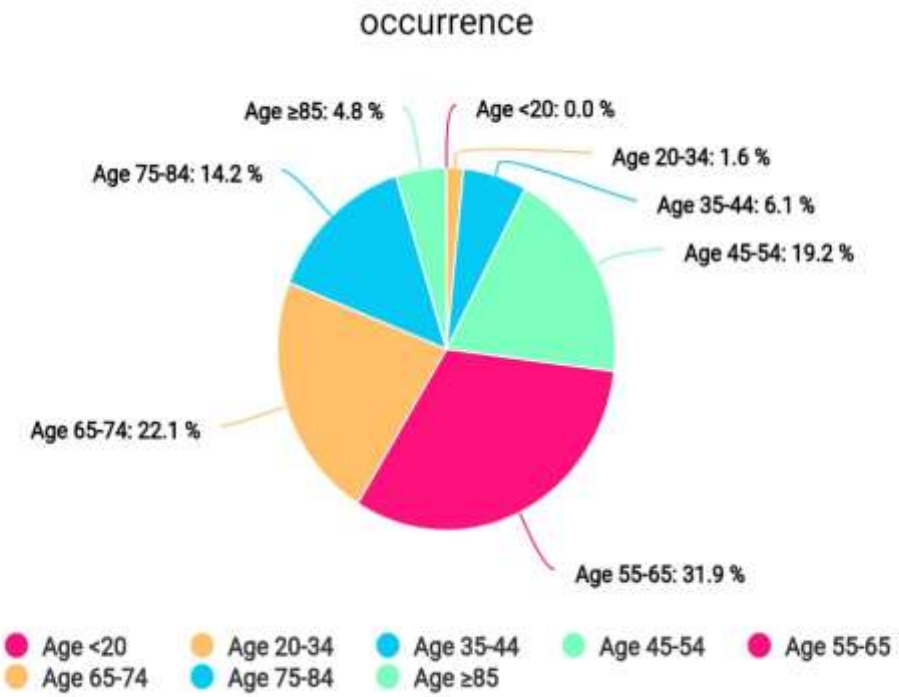

Figure 2. is showing about demographic pattern of irregularities among females on bases of their age. It is mentioned that which aged female is more prone to contraceptives abnormalities and side affects.

Table 1. This table is showing about occurrence of risk factors I females according to their age distribution.

Age (years)	%
<20	0
20–34	1.6
35–44	6.1
45–54	19.2
55–64	31.8
65–74	22.1
75–84	14.2

Table 2. This table is telling about therapeutic applications of vaginal ring in females.

Therapeutic Application
Excessive menstrual bleeding Management (including when associated with uterine fibroids)
Relieving Premenstrual syndrome (PMS) symptoms
Lowering endometriosis pain in women
Giving treatment to various forms of Hemoglobinopathy
Seizures refractory to traditional anticonvulsants
Menstrual hygiene problems in hindered women
Managing endometrial hyperplasia
Vasomotor symptoms (VMS) in menopausal women
After hysterectomy Pelvic pain/dyspareunia of ovarian origin
Relieving ovulatory pain
Treatment for Metastatic breast cancer
Treatment for Metastatic endometrial cancer

Contraceptive

Women who use contraception have more control over personal reproductive health and are able to actively participate in family planning.[8]

Contraceptives associated with Uterine Cancer

The hormonal methods [9] are: Levonorgestrel intrauterine system (LNG IUD), Oral contraceptives ("the pill"), Progestin-only pill, Contraceptive patch, Vaginal ring, Injectable Contraceptive[10], Implant, Long-acting reversible contraceptives (LARCs), Intrauterine device (IUD), Hormonal IUDs. And the Non-Hormonal methods are: Copper IUDs, Sterilization, Tubal ligation, Vasectomy.

Hormonal Contraceptive Methods

1. Levonorgestrel intrauterine system (LNG IUD)-- The LNG-IUS probably slightly minimize the risk of endometrial polyps and endometrial hyperplasia in women with breast cancer taking a drug called tamoxifen.[11] 9144 of the 104,318 women who made up our investigation group had ever used LNG-IUS, whereas 95,174 had never used it, shown in Figure 3. They were every participant in the Norwegian Women and Cancer research.[12] Recent research suggests that the levonorgestrel-releasing intrauterine system (LNG-IUS), which protects carcinoma of the endometrium as well as breast cancer, might additionally avoid ovarian cancer mentioned in figure no.3 . We contrasted the adjusted risks of breast, endometrial, and cancer of the ovaries in LNG-IUS users and those who were not users.[13]

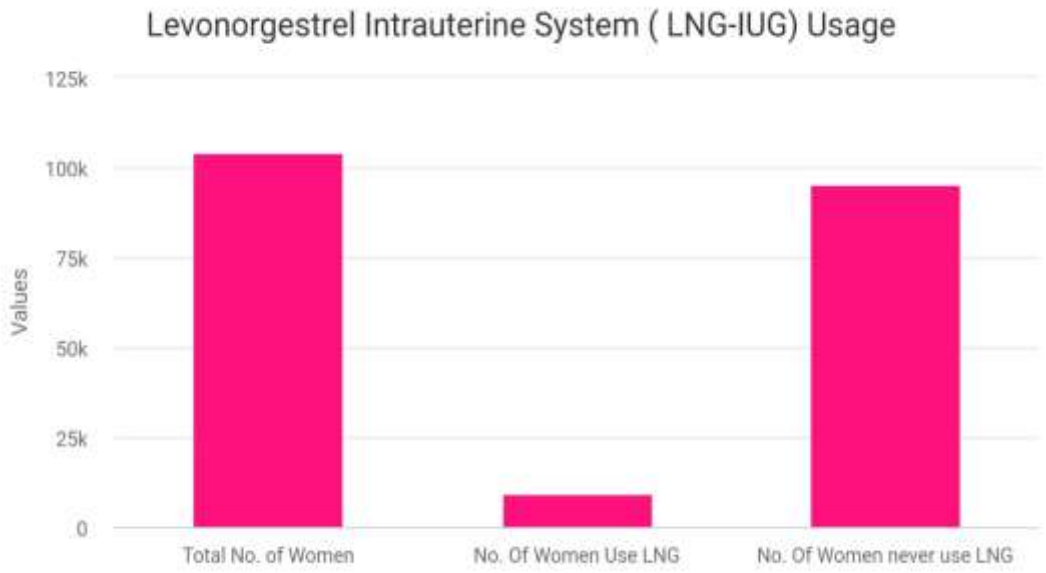

Figure 3. is showing about usage of LNG-IUG (Levonorgestrel intrauterine System- Intra Uterine Devices) in females out of their total areas of interest population.

2. Oral contraceptives ("the pill")/ Combined oral contraception (COC)--The use of combination oral contraceptive (COC), which has been made frequently and consistently demonstrated to reduce the probability of EC with a corresponding decline with increasing duration of use and a residual impact lasting as long as thirty years after the discontinuation of COC, is a vital mitigating factor. The progestin [14] in the pill, which are carried out continuously along with the estrogen, is what causes this favorable impact. Regardless of their pharmacological differences, COC containing various progestins all have the same thing defensive impact on the endometrium. Sequential COC was linked to a rise in EC in young women, illustrating the necessity of contrasting the estrogen therapy with an adequate dose of progestin,[15] Oral contraceptives are used to assess the endometrium of the uterus for estrogen and progesterone levels.

3. Estrogen's Function: Estrogens, which are circulating female hormones, cause the endometrium to thicken; estrogen levels reaching too high can cause the endometrium to expand disproportionately and, ultimately, develop cancer. Serum-binding globulin levels increased substantially adhering to therapy, with variations based on the chemical makeup of the OCs administered.[16] The body's the exposure to estrogens is one of the many acknowledged associated risk factors for this type of cancer. These include:[17]never having been pregnant, Over weighted, no ovulation such as in polycystic ovary syndrome, diabetes mellitus, older age, Usage of tamoxifen for breast cancer

4. Role of Progesterone: A crucial hormone in the endometrium, progesterone inhibits the proliferation attributed to estrogen. Inadequate progesterone will cause unattended estrogen hustle and bustle, which can end up in the growth of carcinogenesis and hypertrophy of the endometrium.[18]

5. Contraceptive patch

The contraceptive patch is a 5 cm by 5 cm adhesives patch that mimics a nicotine patch. Through your skin, it enters your body for distribution of hormones.[19]

Reduce heavy bleeding

The hormones in the contraceptive patch prevent your uterine' lining from accumulating as it normally would. You will have less bleeding than you would during a regular period since you will have less blood and uterine lining to eliminate after a bleed on the patch.. [20]

Reduce the risk of ovarian, endometrial and colon cancer

The combination pill has been the subject of 36 across the globe probes, and the data compiled from these studies revealed that using the combined pill or a contraceptive patch for 10–15 years lowers

the risk of uterine lining cancer by 50%. After quitting the patch or tablet, this advantage may last for up to 30 years. Colon and rectum cancers are 20% more unlikely to appear in people who use a combination pill or patch contraceptives.[20]
The patch's positive aspects is effortless to use, can be used by one single partner and is nearly entirely protective when used correctly, to increase patient compliance, it should only be used once per week and not during sexual activity, its existence is detectable by sight, not affected by contact to water or sweat**,** might alleviate menorrhagia and dysmenorrhea that are not biological in nature**,** may in numerous instances reduce acne**,** due to the estrogen focus. She does it could strengthen bones and lower the incidence of ovarian and uterine malignant tumors as well as innocuous breast illness.[21]

Vaginal ring

A slim, adaptable ring. The lady places the ring within her vagina, where it splits hormones regularly for three weeks. For the fourth week, she uses it. The following week; she places a new ring [8]. The contraceptive vaginal ring, additionally referred to as NuvaRing® or "the ring," is a method of monthly birth control that is typically donned for three weeks before being taken out for one week. The ring contains progesterone as well as estrogen, two naturally occurring hormones, just like oral contraceptives such as pill. The ring excludes ovulation and the release of the egg from the ovary while also affecting the cervical mucus so as to prevent sperm from accessing the egg.[22]

Instructions for inserting the ring

Open the provided pouch or container used for the ring's storage. Place the ring inside the container before you insert it. Pinch the entire ring with your thumbs using hygienic hands.
Carefully use your fingers to insert and gently position the tip inside your vaginal opening. Kindly insert the ring into the vagina with a gentle push until it reaches a comfortable position. Different to a diaphragm or cap, the ring doesn't have to encase the cervix. Still, push it a bit deeper into the vaginal canal if you are to feel it and find it uncomfortable. There's not a right or wrong place to ensure the presence, and it doesn't cause discomfort**.** You should be good to check with your cutlet to see if the ring remains present, and if you are sure of its presence, consult a croaker or nurse, if the ring cannot sense, it cannot become misplaced with in the body. After the ring has been in your vaginal canal for 21 days (equivalent to 3 weeks), it should be removed. This removal should take place within the same timeframe.
It serves as an alternative for women who are unable to use estrogen-based contraceptives, like the combined hormone pill and contraceptive patch and their therapeutic effects are mentioned in Table

Implant

A single, thin rod inserted beneath the skin of a woman's upper arm by a healthcare provider. This type of contraceptive method has a effective duration up to four years [8].The contraceptive implant (Nexplanon) is a thin, pliable rod approximately 4cm in length that a professional inserts beneath the skin of the upper arm. The implant operates by slowly releasing progestogen, a hormone that hinders the **liberty** of eggs from the ovaries into the body. Furthermore, progestogen increase in the viscosity of cervical mucus and a reduction in the thickness of the uterine lining[23].

How is the implant functioning?

The implant gradually releases the hormone progesterone into the bloodstream. It inhibits a woman’s monthly ovulation. by causing an increase in the density of the mucus near the cervix, creating a blockade that hinders the passage of sperm into the uterus. Progestogen exhibits resemblance to the endogenous hormone progesterone. It diminishes the uterus lining's receptivity, making it less conducive to egg fertilization. [23]

Female having no pregnancy until is more prone to Uterine Cancer

Because this is due to the fact estrogen production lowers with childbirth, the less estrogen makes by her body and this decrease the risk of uterine cancer development. In comparison, Women who never

give birth to a child are twice times prone to develop uterine cancer in contrast to those women who have had at least pregnant once. During pregnancy, estrogen levels in the body is reduced.[24]

Sterilization Methods

There are two methods of sterilization:

Tubal ligation: A procedure that put a stop to a woman from becoming pregnant.

It is permanent in happens.

Vasectomy: A surgery that bring a permanent stop to a man from causing pregnancy.

These methods while effective in preventing pregnancy, lead to higher estrogen levels but more Estrogen will lead you towards increase the risk of uterine cancer.[8]

Intrauterine devices (IUDs):

Is the Intrauterine devices endometrial cancer are connected with each other?

The global acceptance of intrauterine devices (IUDs) as a long- term contraceptive system has been on the rise., An IUD have forceful contact endometrial towel grounded on given the settling of IUDs within the uterine filling. By considering the type of device operation this study builds on former work and the duration of operation. The study results suggest that women who use non-hormonal IUDs have a lower liability of developing endometrial cancer. The extent of the reduction in endometrial cancer threat is appreciatively identified with the duration of IUD operation.[25]

Intrauterine devices Related to Uterine cancer

Contraceptive methods which are long-acting and reversible like Intrauterine Devices (IUDs), instigate various, biochemical alterations and immunological alterations in the uterine portion environment that could influencing endometrial cancer (EC) risk.[26]

Hormonal IUDs

Use of hormonal contraceptives has been linked to alterations in women's bone mineral density. It's unclear if those changes raise the chance of fractures in later life. A serious public health concern is osteoporosis. The probability of fracture is elevated by age-related reductions in bone mass, particularly in the wrist, hip, and spine.[27]

Hormonal IUDs: These are occasionally appertained to as LARC (Long- Acting Reversible Contraception) devices, a form of long- lasting birth control. An IUD is a contraceptive device, generally small and T- shaped, fitted into the uterus by a healthcare provider. Hormonal IUDs constructed from plastic and two plastic threads that extend from the cervix.[28]

Uterine malignancy and Hormonal IUDs:

IUS (Intrauterine System), that is a hormonal IUDS comprises a tiny, stretchy a T-like device that your doctor inserts into your womb to emit low quantities of hormones. Levonorgestrel functions by increasing the viscosity of cervical mucus, hindering the movement of sperm towards the fallopian tubes. It also causes a thinning of the uterine lining and defeat the release of an egg during the menstrual cycle. The application of levonorgestrel- releasing intrauterine systems is linked to decrease liability of developing endometrial cancer.

Strategy mechanism

Intrauterine Method

A Hormonal IUDs also called IUS (Intrauterine System) is a small, flexible, T-shaped system that releases low levels of hormones and is placed inside the womb by your healthcare provider.[29]

Devices names[30] Progesterone-releasing intrauterine device and Levonorgestrel-releasing intrauterine device.

Progesterone-releasing intrauterine device:
A synthetic version of the hormone progesterone release by Hormonal IUDs. Progesterone is produced by both the woman's body and the placenta, leading to the cessation of the menstrual cycle and ovulation. Hormonal IUDs, on the other hand, slowly release progesterone over a long period. This gradual release of progesterone ensures the IUD's contraceptive effectiveness for several years. For example: let's consider the Levonorgestrel-releasing intrauterine device.[31]

Device that's produces levonorgestrel intrauterinally
The levonorgestrel-producing intrauterine device provides an extremely efficient form of contraception. It has a strong anti-proliferative action on the endometrium. Levonorgestrel transformed the endometrium under his influence, unaccepted for ovarian estrogens.[32]

Non-Hormonal IUD
Copper intrauterine device (IUD) is a non-hormonal IUD small, T-shaped device made of plastic coated in copper with two threads settled.[29]

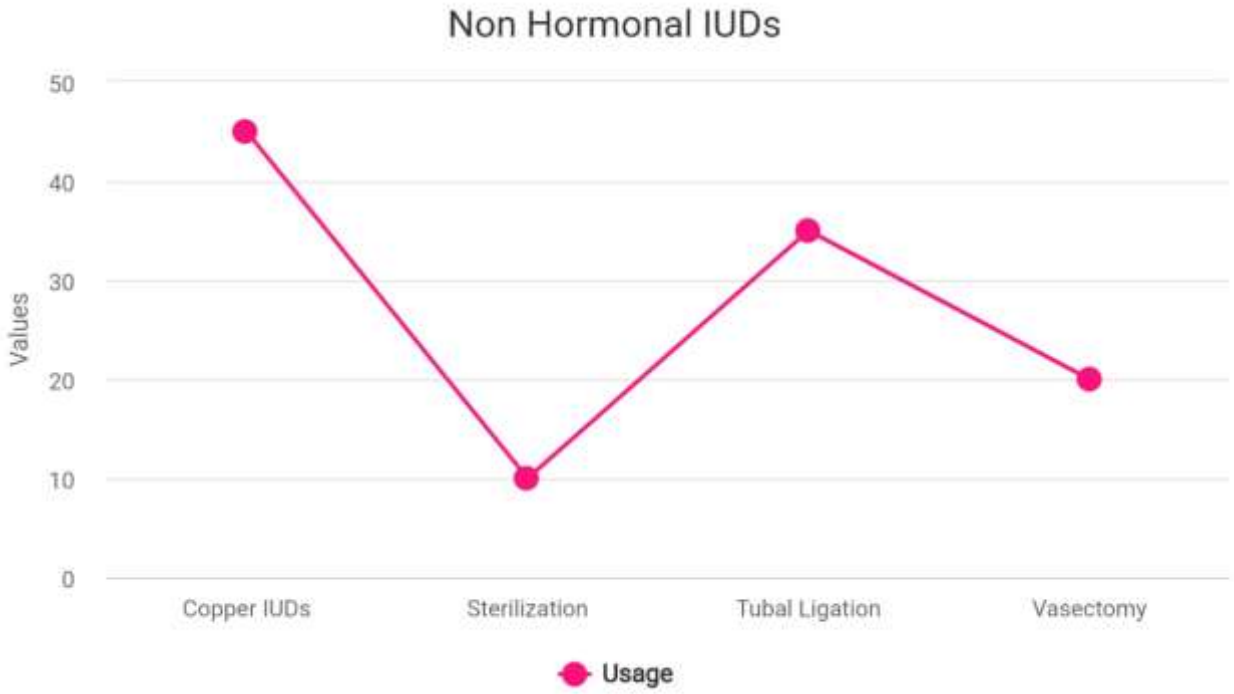

Figure 4. is showing names of non-hormonal IUDs that are more frequently used in % in females.

IUDs of copper:
They increase the inflammatory response, which inflames the endometrium, the lining of uterus. Even if sperm were to fertilize an egg, uterine lining would not fix the fertilized egg and make it harder to developed.[30]

Copper IUD related to Uterine cancer:
Endometrial mitotic activity and estrogen receptor concentrations has been Reduced by the link of Copper-IUD which inhibits endometrial growth, giving protection against endometrial cancer. Cu-IUDs cause chronic inflammation of uterine part of females, which hinders endometrial hyperplasia.[33] Inflammation commonly play a role in promotion of various types of cancer, and there is a hypothesis give a reason for the factors involved in the development of endometrial cancer (EC).[25] Moreover, the copper intrauterine devices (Cu-IUDs) use can lead to the infiltration of numerous immune cells, circling the endometrial gland and This can result in alterations of the

functioning of different components of immune system. Long time use of Cu-IUDs is associates with the reduction in the number of glands in the endometrium.[34]

1. LITERATURE OF REVIEW

The review of different literature has been done for this articles which explain the contraceptives related uterine cancer. Based on a study on the association between modern hormonal contraception and endometrial cancer risk in women by a person [35] on the females of Denmark from 15 to 79 years, gave an outcome that during 21.1 million person-years of monitoring, there were 362 incidence endometrial malignancies among non-users and 187 among active users of hormonal contraception. Among current or recent users, combined oral contraceptives containing gestodene, desogestrel, or levonorgestrel accounted for nearly two-thirds of all hormonal contraception use.

Following another study on the risk of cervical cancer with estrogen, progestin contraceptives by an investigator [36] concluded that the human papilloma virus (HPV), which causes cervical cancer, may be encouraged by steroid contraceptive hormones. HPV-DNA sequences inside transcriptional regulatory areas may bind to these hormones, and the hormones may also influence cell death.

A research conducted by researchers [37] by collecting the data in eight US regions on the risk of ovarian cancer and intrauterine contraception determined that Compared to women who have never used intrauterine contraception, there is a statistically significant decrease in the chance of acquiring cervical cancer in women who use it. Furthermore, the risk of developing endometrial cancer was about halved for women who had used intrauterine contraception compared to those who did not.

An investigation carried out by a researcher [38] on examine the impact of hormonal contraceptive tablets on cancers of the uterus and ovaries. Information was gathered from questionnaires and samples from fifty cases of ovarian and uterine cancer were used to gather data. The samples were taken from the oncology Center in Diwaniyah as well as from several hospitals and cancer centers in the surrounding provinces. Hormonal medications are the most common type of contraception. Birth control tablets and contraceptives are made to employ either progestin or estrogen. The recent study's findings demonstrated that hormonal contraceptive tablets can lower the risk of ovarian and uterine cancer. A study [39] on the epigenetic theory that a person's usage of oral contraceptives helps prevent ovarian cancer has final outcome is that the risk of developing ovarian cancer decreases with the duration of contraceptive usage, with the most benefit being shown in women who have been using the pill for over ten years.

2. DISCUSSIONS

Subheadings may be used to organize this section. This should give a clear and simple explanation of the experimental findings, their meaning, and any inferred experimental implications.

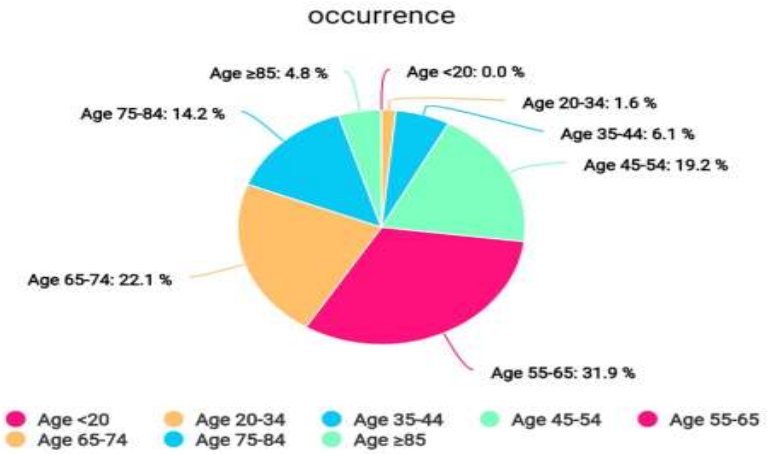

Figure 2. is showing about demographic pattern of irregularities among females on bases of their age. It is mentioned that which aged female is more prone to contraceptives abnormalities and side effects.

3. CONCLUSION

The Conclusion is that, the intrauterine cancer and contraceptive association is a difficult and emerging field of research. Healthcare professionals and researchers should work with collaboration to confirm contraceptive effectiveness. Meanwhile, some studies give suggestion of potential associations, so there is more investigation are needed to make a clear causal links. Ongoing surveillance and further researches will help in understandings of these potential risks.

Funding: There is not any external funding provided by any institute and agency or NGO for facilitation of this article performance

Acknowledgments: The author is dedicating this article work to his parents and teachers and institute who gave him guidance for its completion.

Declaration of Interest:
It is declared that the AI tools and AI-associated technologies were not used in the writing process, to analyze and draw insights from data as part of the research process.

Submission Declaration and Verification:
It is declared that this work has not been published previously.

REFERENCES

1. AKU. *Gynaecological Cancers | Prevention and Treatment* 2020; Available from: https://hospitals.aku.edu/pakistan/AboutUs/News/Pages/gynecological-cancers-prevention-and-treatment.aspx.
2. Holman, L., Lu, K, Glob. libr. women's med, *The Epidemiology of Endometrial Cancer*. GLOWM, 2012.
3. Heywood, J.S., *Prevention of Ovarian and Endometrial Cancer byCombined Oral Contraceptives: A Demographics Study*, in *Keck Science Department Of Claremont McKenna, Pitzer, and Scripps Colleges*. 2017, Claremont Colleges: Scholarship @ Claremont. p. 35.
4. ASCO. *Do Birth Control Pills Impact My Cancer Risk?* 20,2022 2022; Available from: https://www.cancer.net/blog/2022-10/do-birth-control-pills-impact-my-cancer-risk#:~:text=About%2066%2C000%20people%20will%20be,longer%20the%20pill%20is%20taken.
5. Brinton, A.S.F.a.L.A., *Cancer Progress and Priorities: Uterine Cancer.* Cancer Epidemiol Biomarkers Prev., 2018
6. ASCO. *Uterine Cancer: Introduction*. 2022; Available from: https://www.cancer.net/cancer-types/uterine-cancer/introduction.
7. OCRA. *Endometrial Cancer vs Uterine Cancer*. 2023; Available from: https://ocrahope.org/news/is-endometrial-cancer-the-same-as-uterine-cancer/#:~:text=Endometrial%20cancers%20develop%20from%20the,They%20are%20rare.
8. Plus, M. *Birth Control Also called: Contraception*. 2022; Available from: https://medlineplus.gov/birthcontrol.html#.
9. Cooper., O.M.B.M.S.S.D.B., *Contraception*. 2023, StatPearls Publishing: National Library of Medicine.
10. author, R.J.a.S.M., *Contraceptive Methods: Needs, Options and Utilization.* J Obstet Gynaecol India, 2012. **61(6): 626–634.** .
11. Sally AD Romero, K.Y., Martha Hickey, and H Irene Sucorresponding *Levonorgestrel intrauterine system for endometrial protection in women with breast cancer on adjuvant tamoxifen.* Cochrane Database Syst Rev., 2020.
12. Mie Jareid , J.-C.T., Morten Aarflot , Hege M Bøvelstad, Eiliv Lund , Tonje Braaten *Levonorgestrel-releasing intrauterine system use is associated with a decreased risk of ovarian and endometrial cancer, without increased risk of breast cancer.* Gynecol Oncol, 2018. **149(1):127-132**.

13. Anne Gompel MD, P., *Progesterone and endometrial cancer.* Elsevier, 2020. **69**: p. 95-107.
14. MD, A.M.M.M.a.T.A.L., *Endometrial hyperplasia.* 2010. **27**(4): p. 199-214.
15. Anderson, M. *The pill and cancer: Is there a link?* . 2016; Available from: https://www.mdanderson.org/publications/focused-on-health/birth-control-pill-and-cancer-risk.h28Z1590624.html?
16. Wiegratz, I., et al., *Effect of four different oral contraceptives on various sex hormones and serum-binding globulins.* 2003. **67**(1): p. 25-32.
17. Endocrinology, S.f. *Endometrial cancer*. 2021; Available from: https://www.yourhormones.info/endocrine-conditions/endometrial-cancer/.
18. J. Julie Kim, P.D.a.E.C.-D., M.D, *Role of Progesterone in Endometrial Cancer.* Semin Reprod Med. , 2010. **28(1): 81–90**.
19. inform, N. *Contraceptive patch* 2022; Available from: https://www.nhsinform.scot/healthy-living/contraception/contraceptive-patch#:~:text=The%20contraceptive%20patch%20is%20a,works%20in%20the%20same%20way.
20. SH:24. *Health benefits and risks of the patch*. Available from: https://sh24.org.uk/contraception/patch/health-benefits-risks.
21. Dr. Liji Thomas, M. *Advantages and Disadvantages of the Contraceptive Patch*. 2019; Available from: https://www.news-medical.net/health/Advantages-and-Disadvantages-of-the-Contraceptive-Patch.aspx.
22. St. Louis, M., *Contraceptive Vaginal Ring FACT SHEET.* Washington University in St. Louis School of Medicine.
23. inform, N. *Contraceptive implant*. 2023; Available from: https://www.nhsinform.scot/healthy-living/contraception/contraceptive-implant#:~:text=The%20contraceptive%20implant%20is%20a,and%20thins%20the%20womb%20lining.
24. Society, C.C. *Risk factors for uterine cancer*. Available from: https://cancer.ca/en/cancer-information/cancer-types/uterine/risks#:~:text=Women%20who%20never%20give%20birth,risk%20of%20developing%20uterine%20cancer.
25. Ashley S. Felix, M.M.G., Carlo La Vecchia, Christina M. Nagle, Xiao Ou Shu, Elisabete Weiderpass, Hans Olov Adami, Shirley Beresford, Leslie Bernstein, Chu Chen, Linda S. Cook, Immaculata De Vivo, Jennifer A. Doherty, Christine M. Friedenreich, Susan M. Gapstur, Dierdre Hill, Pamela L. Horn-Ross, James V. Lacey, Fabio Levi, Xiaolin Liang, Lingeng Lu, Anthony Magliocco, Susan E. McCann, Eva Negri,Sara H. Olson, Julie R. Palmer, Alpa V. Patel, Stacey Petruzella, Jennifer Prescott, Harvey A. Risch, Lynn Rosenberg25, Mark E. Sherman, Amanda B. Spurdle, Penelope M. Webb, Lauren A. Wise, Yong-Bing Xiang, Wanghong Xu, Hannah P. Yang, Herbert Yu, Anne Zeleniuch-Jacquotte and Louise A. Brinton, *Intrauterine devices and endometrial cancer risk: A pooledanalysis of the Epidemiology of Endometrial CancerConsortium.* International Journal of Cancer, 2015.
26. Ashley S. Felix, M.M.G., Carlo La Vecchia, Christina M. Nagle, Xiao Ou Shu,, et al., *Intrauterine devices and endometrial cancer risk: a poole analysis of the Epidemiology of Endometrial Cancer Consortium.* Int J Cancer, 2015. **136(5): E410–E422**.
27. Lopez, L.M., et al., *Steroidal contraceptives: effect on bone fractures in women.* 2014(6).
28. Lowa, U.o. *Hormonal (progestin) intrauterine devices* 2021; Available from: https://uihc.org/educational-resources/hormonal-progestin-intrauterine-devices#:~:text=They%20may%20be%20called%20LARC,not%20need%20to%20be%20treated.
29. Childrens, N. *Birth Control: Non-Hormonal Copper Intrauterine Device (IUD)*. 2022; Available from: https://www.nationwidechildrens.org/family-resources-education/health-wellness-and-safety-resources/helping-hands/birth-control-non-hormonal-

iud#:~:text=The%20non%2Dhormonal%20copper%20intrauterine,does%20not%20have%20any%20hormones.
30. Clinic, C. *Intrauterine Device (IUD)*. 2022; Available from: https://my.clevelandclinic.org/health/treatments/24441-intrauterine-device-iud.
31. Higginbotham, V. *Hormone Releasing Intrauterine Devices*. 2019; Available from: https://embryo.asu.edu/pages/hormone-releasing-intrauterine-devices#:~:text=IUDs%20release%20of%20the%20hormone,that%20contribute%20to%20preventing%20pregnancy.
32. T Luukkainen , P.P., J Toivonen, *Progestin-releasing intrauterine systems* Semin Reprod Med, 2001.
33. Nicole Minalt, M.A.C., MD, MS Grace M. Yedlicka, BSN Sophia Joseph, BA Sharon E. Robertson, MD, MPH Lisa M. Landrum, MD, PhD Jeffrey F. Peipert, MD, PhD *Association between intrauterine device use and endometrial, cervical, and ovarian cancer: an expert review*. AJOG, 2023. **229**(2).
34. Che Jia-Hui , Y.X.-Y., *Effects of Copper-Containing Intrauterine Devices on the Endometrium* Reproductive and Developmental Medicine, 2021. **05 (01): 38-43**.
35. Iversen, L., et al., *Contemporary hormonal contraception and risk of endometrial cancer in women younger than age 50: A retrospective cohort study of Danish women.* Contraception, 2020. **102**(3): p. 152-158.
36. GADDUCCI, A., S. COSIO, and F. FRUZZETTI, *Estro-progestin Contraceptives and Risk of Cervical Cancer: A Debated Issue.* 2020. **40**(11): p. 5995-6002.
37. Castellsagué, X., W.D. Thompson, and R. Dubrow, *Intra-uterine contraception and the risk of endometrial cancer.* 1993. **54**(6): p. 911-916.
38. Al-kurdy, M., et al., *Determine the Effects of Hormonal Contraceptive Pills on Ovarian and Uterus Cancer*. 2024.
39. Avramenko, A. and J. Flanagan, *An epigenetic hypothesis for ovarian cancer prevention by oral contraceptive pill use*. Clinical Epigenetics, 2023. **15**.