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SYSTEMIC REVIEW

Gynaecological Polyps Causing Infertility - a systemic review

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ABSTRACT

Background: Polyps of female reproductive tract are found in about 7.8-50% of women. Endometrial polyps are commonly located at the fundal or the tubocornual region. They mechanically affect female's fertility and disturbs the normal cellular function due to chronic inflammation. To rule out sub clinical endometrial hyperplasia or cancer, endometrial curettage is often recommended. Cervical polyps may grow during pregnancy or mucorrhoea.
Aim: To highlight updates to the epidemiology, clinical presentation and diagnostic techniques for gynaecological polyps.
Study design: Systemic review
Methods: During December 2020 we searched Google scholar, Pub med, Medscape, Web of Science, Scientific Information Database and Magiran research articles from 2010 -2020. The selected articles identified through electronic search were 60 articles and 50 were selected for the review.
Results: Endometrial polyps are the most frequently diagnosed gynaecological polyp, their prevalence ranging from 7.8% to 50%. They are implicated in about 50% of cases of abnormal uterine bleeding and 35% of patients presenting with infertility. The developments of high-resolution 2D and 4D ultrasound, contrast enhanced sonography and hysteroscopy helps in diagnosing polyps efficiently. In certain cases, when hysteroscopy cannot be performed sonohysterography and ultrasonography can be used for screening. Hysteroscopy is the gold standard technique for the diagnosis of gynaecological polyps and histopathology is essential for the ultimate diagnosis and exclusion of malignancy.
Conclusions: The review of literature suggest that the gynaecological polyps are one of the most common cause of abnormal uterine bleeding and have strong association with infertility as they interfere with implantation of an embryo. Polyps can be confidently diagnosed on ultrasound. Other imaging techniques may provide additional information about the details of the anatomy of female reproductive tract and the polyp itself.
Keywords: Endometrial polyp, Cervical polyp, Vaginal/vulvar polyp, Infertility, Ultrasonography, Sonohysterography,.

INTRODUCTION

The widespread use of ultrasound in gynecological examination has caused polyps of female genital tract to be diagnosed more frequently than were previously. For the initial evaluation of all uterine pathologies transvaginal ultrasound is considered as a first line practical approach whereas the hysteroscopy offers a better diagnostic value generally for all uterine pathologies and specifically for uterine polyps[1]. Endometrial polyp is defined as a localized hyperplastic overgrowth of endometrial glands and stroma. They present with symptoms such as menorrhagia, intermittent/postmenopausal bleeding and infertility. Endometrial polyps are most common gynaecological polyps. They are found in 25% cases of AUB and in 35% cases with infertility[2]. The transvaginal ultrasound is used as primary approach for the diagnosis of endometrial polyps. The outgrowths of columnar epithelium of the cervix is termed as cervical polyps. They are more frequent in parous or postmenopausal females and about 60 - 70% of cervical polyps are asymptomatic [3]. Symptomatic polyps are more frequently diagnosed in premenopausal females and may cause symptoms such as intermittent bleeding, post-coital bleeding or post-menopausal bleeding. The fibro-epithelial polyps are hormone sensitive common lesions which typically occurs in obese women, its incidence is estimated to be 46% in the general population[4].

These polyps are located in vulvovaginal region and can manifest in female during reproductive period, pregnancy or even in premenopausal females who are on HRT.

MATERIAL AND METHODOLOGY

Search strategy: International {Google scholar, PubMed and Web of Science (WOS)} and National {Magiran and Scientific Information Database} databases were searched for related observational studies which were published till 2020 Dec.

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Study selection: The selected articles picked out through electronic search comprises the period from 2010 to 2020. The articles were reviewed in depth for a more detailed analysis. Databases reported almost 60 articles and out of them 50 articles were selected for the review.

DISCUSSION

The aim of this systematic review is to highlight the latest updates to the epidemiology, clinical presentation and various diagnostic techniques for gynaecological polyps providing best guide to the health-workers in their clinical decisions. It also highlights prevalence of infertility in patients with gynaecological polyps. We have analyzed almost 60 publications that emphasized on the topics related to female reproductive tract polyps, their epidemiology, clinical presentation, imaging techniques and association with infertility. With recent advancement in imaging techniques such as 3-dimensional ultrasound, clinician is able to diagnose polyps and can provide information about their specific anatomy and localization. Other imaging modalities also helps the clinicians in diagnosing polyps more efficiently. Strong association is seen to occurs between polyps and infertility as infertility is identified as prevalent among 35% of patients with polyps.

It arises from a Greek word "polypus" which means "many feet". A polyp is defined as a benign polypoidal growth which can arise from any mucus membrane in the body. Gynaecological polyps grow mainly in the uterus and the cervix. They rarely occur in the vagina. They are categorized on the basis of their type, location, and presence or absence of a stalk[5].

Types of gynaecological polyps

Endometrial polyps: The most commonly diagnosed gynaecological polyps are the endometrial polyps. It is an abnormal growth containing endometrial glands, stroma and blood vessels projecting from the lining of the uterus that may be large or small enough to occupy the entire uterine cavity. Endometrial polyps can be prevalent during reproductive or postmenopausal females[6]. Endometrial polyps are considered hyperplastic growths but are usually benign[2]. Gross morphological appearance of an

endometrial polyp is a smooth, cylindrical or spherical structure which may be tan to yellow in colour.

Cervical polyps: They are second most commonly occuring polyps after endometrial polyps and are the most common benign lesion of the cervix which arise within the endocervical canal. The papillary proliferations of epithelial tissue around a fibro-vascular stromal core which may have glandular or squamous epithelium constitutes cervical polyp[7]. Cervical polyp varies in size from 5mm to 50 mm and appears as cherry red to purplish red in color. They are friable, soft and pedunculated on gross examination which may readily bleed on touch[8].

Vaginal/valvar polyps: They are very rare hormonal dependent benign disorder. They occur in young to middle-aged women, or in pregnant females or in females on hormonal replacement therapy[9].

Epidemiological factors

Endometrial polyps: They are the most commonly reported gynaecological polyp. Their prevalence ranges from 7.8% to 50% [10]. The prevalence of endometrial polyp rises with age and menopause. Asymptomatic polyps are mostly discovered during routine physical examination or investigations when women come for infertility evaluation. According to another study, they account for 7.8% to 34.9% in patients attending clinics with AUB[5].

Cervical polyps: Cervical polyps are the second most commonly diagnosed polyps next to endometrial polyps. Levy et al. stated that the endo-cervical polyps occur in about 2-5% of the population[7].

Vaginal/vulva polyps: Vaginal or vulvar polyps are the rare gynaecological polyps[9].

Topographical classification of polyps: The basic difference between cervical and endometrial polyps is their localization. The first step to categorize gynaecological polyps is on the basis of their topography.

Endometrial polyps: Endometrial polyps are located inside the uterine cavity[7]. Endometrial polyps can be located at any site within the endometrial cavity but most frequently in anterior or posterior walls and the fundus. Abnormal uterine bleeding occurs in approximately 68% of women and usually more commonly seen in women during premenopausal period[11].

Cervical polyps: Cervical polyps can be ecto-cervical, present on the outer surface of the cervix or endocervical, present inside the cervical canal demarcated by the transformation zone[7]. More common ones are the endocervical polyps and presents in premenopausal females. Cervical polyps are mostly asymptomatic lesions which are benign in nature. They are symptomatic mostly in postmenopausal women. Symptomatic cervical polyps commonly manifest as intermenstrual, post-coital or postmenopausal bleeding[12].

Vaginal polyps: The commonest clinical presentation of fibro-epithelial polyp is a painless mass. Other symptoms include pruritis and malodorous discharg[13].

Stalk formation: Another way to categorize gynaecological polyps is on the basis of presence or absence of a stalk. Pedunculated polyps are polyps with narrow elongated stalk and sessile polyps are the polyps with no stalk. The more commonly occurring polyps are pedunculated polyps.

Histological type

Endometrial polyps: Endometrial polyps are marked by irregular glands, fibrotic stroma and thick blood vessels. In rare cases, they can be atrophic, hyperplastic or carcinomatous[7].

Cervical polyps: Cervical polyps are characterized by a central fibro-vascular core of stromal cells. These stromal cells are surrounded by a papillary proliferations of cells. These cells may be composed of squamous or glandular epithelium. Squamous metaplasia is commonly seen at the tip of the polyp[7].

Vaginal polyps: They are characterized as tubulo-squamous in nature[9].

Genetics and predisposition: The most extensively studied etiological factor is genetic modifications. Other possible etiological factors seen in the published studies are metabolic, drug induced, environmental factors, age, obesity, hypertension, diabetes mellitus, steroid hormone receptors and menopause status[14]. Few studies also suggest genetic predisposition of cervical polyps as they are associated with inflammation[7].

Pathogenesis: The exact pathogenesis of gynaecological polyps is vague.

Endometrial polyps: Pathogenesis of endometrial polyps involves glandular, menopause independent AB DNA fragmentation factor 40, 45 (DFF40), (DFF45) and Bcl-2 overexpression (Fig. 1)[15]. Miranda et al. concluded that in polyp of tamoxifen-treated women, the expression of Ki-67 is significantly higher as compared to those using no hormone[16].

Cervical polyps: The pathophysiology is not clearly understood. The possible pathogonesis include chronic inflammation, hormonal stimulation or cervical blood vessel congestion[17].

Vaginal/vulvar polyps: The pathogenesis of fibro-epithelial polyp is uncertain. Several cases have suggested that a hormonal influence may be a predisposing condition for developing fibro-epithelial polyp[13].

The effect of endometrial polyps on the endometrium: Increased production of glycodelin associated with endometrial polyps reduces the blood flow to endometrial lining which results in damage of implantation and increases chances of miscarriages. Due to surface erosion and vascular fragility, AUB is most frequent symptom reported in these cases. Endometrial polyps appear as chronic inflammation or endometrial erosion and is associated with vascular dilatation on hysteroscopy. Ischemic necrosis may develop at the apex of large polyps[18].

Polyps in premenopausal women

Transvaginal ultrasound: In routine gynaecological examinations, the wide use of transvaginal ultrasound has played a key role to diagnose polyps with increased accuracy. For the diagnosis of endometrial polyps, baseline imaging technique used is transvaginal ultrasonography. Transvaginal imaging is performed on the 10th day of the menstrual cycle to obtain more accurate results as the endometrium is thinnest and the endometrial polyp will appear more prominent. Transvaginal imaging is done by penetrating a trans-vaginal ultrasound probe through the vagina in order to visualize the uterine cavity. On ultrasonography, endometrial polyps appear as a hyper-echogenic lesion with regular contours[11]. According to Babacan et al., transvaginal ultrasound has sensitivity and specificity of 19%–96% and 53%–100% to diagnose endometrial polyps[1]. Fig. 2 demonstrates endometrial polyp on TVS[19]. Sonographic appearance of cervical polyps is well-circumscribed masses within the endo-cervical canal which may be hypoechoic or echogenic[20]. Fibro-epithelial polyps of vagina appear on ultrasound as circumscribed ovoid homogenous mass[21].

Colour-flow Doppler: Colour Doppler demonstrates a single feeding vessel which is salient feature of endometrial polyps (Fig. 3)[19]. A study carried out by Metello and Jimenez concluded that to diagnose polyps, power doppler has increased sensitivity and specificity around 97% and 95% respectively[22].

Saline infusion sonography: The addition of intrauterine contrast helps out to outline small polyps which are missed on greyscale transvaginal ultrasound. In year 2018, Fadl et al reported that for the diagnosis of endometrial polyps, saline infusion sonohysterography provide a better diagnostic accuracy than the transvaginal ultrasound[23]. On saline infusion sonography, they appear as smooth echogenic masses[19].

Hysteroscopy: Hysteroscopy is a gold standard technique for diagnosis and treatment of gynaecological polyps. It is efficient diagnostic technique in premenopausal as wells as in the postmenopausal females[11]. After excision of a polyp via hysteroscope, endometrial curettage is performed to exclude endometrial hyperplasia and cancer via histopathological examination[12]. In year 2014, according to a study carried out to compare TVS and hysteroscopy in the diagnosis of uterine pathologies by Babacan et al. which stated that hysteroscopic evaluation offers better diagnostic value in diagnosing all uterine pathologies, particularly the gynaecological polyps[1]. A comparison

of TVS, saline infusion sonohysterography and hysteroscopy in diagnosis of endometrial pathology in women with AUB was published in 2020 which concluded that in patients presenting with AUB, saline infusion sonohysterography was superior to TVS and has a comparable diagnostic accuracy to hysteroscopy in detecting uterine pathologies. (Table 3-7) In countries such as Africa, for diagnosis of endometrial pathologies saline infusion sonohysterography is considered as the first line investigation and diagnostic hysteroscopy is reserved for patients with inconclusive saline infusion sonohysterography report[24,25].

Histopathology: It is diagnostic imaging technique for evaluation of polyps.

Endometrial polyps: Endometrial polyps should be confirmed microscopically by the histopathologist. Under microscopic examination, dense fibrous stromal tissue is visualized as compared to the surrounding endometrium and parallel arrangement of endometrial gland long axis to the surface epithelium is characteristic for polyps. The majority of endometrial polyps do not respond to hormonal stimuli. They exhibit cystic endometrial hyperplasia throughout the menstrual cycle and do not shed during menstruation[26]. (Table 1)

Cervical polyps: On histopathology, in addition to stromal cells cervical polyps exhibit vascular connective tissue covered by the papillary proliferation of cells. The epithelial cells may be squamous, columnar or squamo-columnar. Microscopically, histological patterns are vascular, inflammatory, mucosa, pseudo-decidual, fibrous, a mixture of cervical and endometrial, and pseudosarcomatous[27] (Table 2).

Vaginal polyps: On histopathologic examination, it is seen as a fibrocollagenous tissue in the stroma with thick blood vessels and perivascular infiltrate. This chronic inflammatory infiltrate is covered with stratified squamous epithelium of the vulva[28].

Diagnosis and management of polyps in infertility: Gyanecological polyps may cause irritation of the lining of the uterus therefore they have strong association with infertility as they interfere with implantation of an embryo. The location of a polyp is important in addressing fertility issues.

Endometrial polyps & infertility: Endometrial polyps are frequently seen in sub-fertile women. They are acquired in nature and are directly related to decreased fertility. The prevalence of endometrial polyps is up to 32% in infertile population[29]. In women with unexplained infertility, the reported frequency of endometrial polyps diagnosed by hysteroscopy is to be between 16.5% - 26.5% [30]. One hypothesis suggests that mechanical obstruction of the tubal ostia caused by an endometrial polyp impairs sperm or the embryo from entering into the uterine cavity. The surgical excision of endometrial polyps located at the utero-tubal junction reveals best pregnancy outcomes in case of intrauterine insemination cycles and in ovulation induction[18].

Cervical polyps & infertility: The association between infertility and cervical polyps depends on location where the polyp is placed. Polyps located high up in the cervix can block the opening of the cervix and hinders fertilization[31].

Spontaneous conception after polypectomy: Studies have revealed increased pregnancy rate in infertile women is reported after hysteroscopy guided polypectomy, particularly after the removal of tubo-cornual polyps[11].

IVF and ICSI after polypectomy: Removal of remove endometrial polyps is generally prescribed before commencement of in-vitro fertilization or intra-cytoplasmic sperm injection treatment. Moon et al. proposed that ultrasound guided polypectomy using trans-cervical sharp curettage in women undergoing controlled ovarian hyperstimulation or even at the time of ovum pick-up is safe and does not impact the pregnancy outcome[32].

Strength and limitations: This systemic review provides an in-depth view of gynaecological polyps that a reader might want to study, and the detail that we have compiled is extremely valuable. However, our study had several limitations as we focused more on comparing different diagnosing modalities rather than focusing on ultrasonography only as it is first-line diagnostic modality for diagnosing fibroids.

Interpretations: Endometrial polyps are the most commonly diagnosed gynaecological polyp. They are prevalent in 50% cases of AUB and 35% patients with infertility. The developments of high-resolution 2-dimensional and 4-dimensional ultrasound, contrast enhanced sonography and hysteroscopy helps the clinicians in detecting polyps efficiently. Hysteroscopy is the gold standard and histopathology is essential investigation for the ultimate diagnosis of polyps and exclusion of malignancy.

CONCLUSION

The review of literature suggest that the polyps are one most frequent cause of AUB and infertility. They are efficiently diagnosed on ultrasounography with doppler imaging. Other imaging techniques provides additional information about the anatomy of the female reproductive tract and the polyp itself. Hysteroscopy and histopathological evaluation is considered as a gold standard for diagnosis of gynaecological polyps. Furthermore, gyanecological polyps have strong association with infertility as they interfere with implantation of an embryo by irritating the lining of the uterus.

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Table 1. Histopathological diagnosis of endometrial polyps[39]

HISTOPATHOLOGY OF ENDOMETRIAL POLYPS	FREQUENCY	PERCENTAGE
Benign endometrial polyp	28	40%
Endometrial hyperplastic glandular polyp	8	12%
Atrophic polyp	5	7%
Functional Polyp	12	17%
Hyperplastic polyp with complex hyperplasia	2	3%
Hyperplastic polyps with atypia	1	1.0%
Leiomyomatous polyp	8	12%
Polyp with simple hyperplasia	6	8%

Table 2. Histopathological diagnosis of cervical polyps[40]

HISTOPATHOLOGY OF POLYPS	FREQUENCY	PERCENTAGE
Endocervical mucosal polyp	22	55%
Leiomyomatous polyp	12	30%
Endocervical glandular polyp	6	15%
Total	40	100%

Table 3. TVS, SIS, and diagnostic hysteroscopy findings of premenopausal and postmenopausal women. [37]

	Frequency: n (%)		
	TVS	*SIS*	*Diag. Hysteroscopy*
Normal	27 (67.5)	8 (20.0)	6 (15.0)
Sub mucosal fibroid	7 (17.5)	19 (47.5)	21 (52.5)
Endometrial polyp	6 (15)	8 (20.0)	8 (20.0)
Cervical polyp	0 (0.0)	1 (2.5)	1 (2.5)
Endometrioid cyst	0 (0.0)	2 (5.0)	2 (5.0)
Synechiae	0 (0.0)	3 (7.5)	6 (15.0)
Cervical stenosis	0 (0.0)	3 (7.5)	3 (7.5)
Mullerian duct anomalies	0 (0.0)	0 (0.0)	1 (2.5)

Table 4. Sensitivity and specificity of TVS versus hysteroscopy in evaluation of endometrial pathology in pre- and postmenopausal women [37]

Pathology	*Sensitivity*	*Specificity*	*PPV*	*NPV*	*DA*
Overall	38.2	100	100	22.2	47.5
Normal	38.2	100	100	22.2	47.5
Submucosal Fibroid	33.3	100	100	57.6	65.0
Endometrial polyp	75.0	100	100	94.1	95.0
Synechia	0	100	-	85.0	85.0
Endometrial cyst	0	100	-	95.0	95.0

Table 5. Sensitivity, specificity PPV and NPV of SIS versus hysteroscopy. [37]

Pathology	Sensitivity	Specificity	PPV	NPV	DA
Overall	92.1	83.3	96.9	62.5	90.0
Normal	94.1	100	100	75.0	95.0
Sub mucosal fibroids	90.5	100	100	90.5	95.0
Endometrial polyp	100	100	100	100	100
Endometrioid cyst	100	100	100	100	100
Synechiae	50	100	100	91.9	92.5

Table 6. Overall sensitivity, specificity, PPV, NPV, and accuracy of TVS versus SIS. [37]

Pathology	Sensitivity	Specificity	PPV	NPV	Accuracy
TVS	38.2	100	100	22.2	47.5
SIS	92.1	83.3	96.9	62.5	90.0

Table 7. Comparison of the sensitivity and specificity of SIS and TVS in detecting individual endometrial pathologies. [37]

	SIS					TVS				
Pathology	Se.	Sp.	PPV	NPV	DA	Se	Sp.	PPV	NPV	DA
Normal	94.1	100	100	75.0	95.0	38.2	100	100	22.2	47.5
Sub mucosal fibroids	90.5	100	100	90.5	95.0	33.3	100	100	57.6	65.0
Endometrial polyp	100	100	100	100	100	75.0	100	100	94.1	95.0
Endometrioid cyst	100	100	100	100	100	0	100	-	85.0	85.0
Synechiae	50	100	100	91.9	92.5	0	100	-	95.0	95.0

Fig. 1 Diagrammatic summary of polyp etiologies[38]

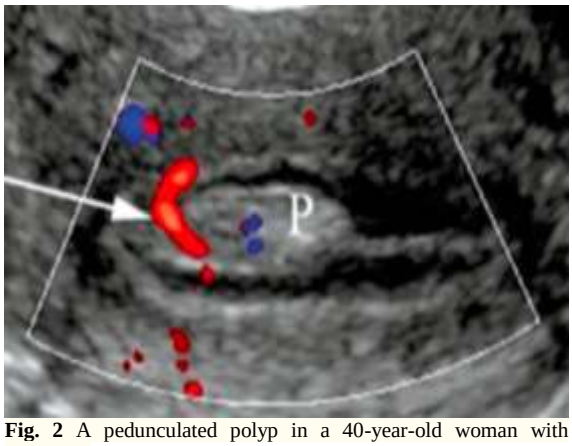

Fig. 2 A pedunculated polyp in a 40-year-old woman with infertility.
3-D SIS and colour Doppler demonstrates a solitary, smooth, well-defined, uniformly echogenic endometrial lesion (P) arising from the anterior wall with a single feeding vessel (arrow)[31]

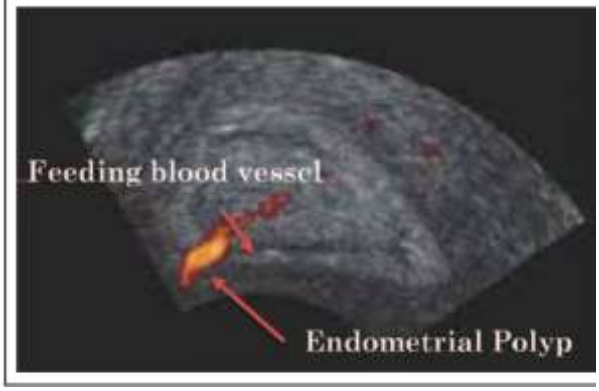

Fig. 3 Power Doppler or colour-flow ultrasound image showing the feeding blood vessel characteristic of an endometrial polyp. Adapted from Lieng et al.78 with permission from Professor Marit Lieng, Department of Gynaecology, RESearch Centre for Obstetrics and Gynaecology (RESCOG), Oslo University Hospital, Norway[34]