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ORIGINAL RESEARCH

Risk Factors for Adnexal Masses in Females Less Than 45 Years

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ABSTRACT

Background: This study was conducted to examine the risk factors for adnexal masses in females less than 45 years, study the distribution of different types of adnexal masses in the study population, and to identify risk factors for benign and malignant ovarian tumors andendometriosis. **Methods:** This was a hospital-based case control study conducted among 135 females of age less than 45 years who presented with sonographic evidence of adnexal masses to the Department of Obstetrics and Gynecology at SAT Hospital, Trivandrum, a government institution, after obtaining clearance from the institutional ethics committee and written informed consent from the study participants. **Results:** Oral contraception was found to be a protective factor (OR-.230, p-value = 0.022) in the development of different adnexal masses. Dysmenorrhea was also found to be a protective factor while applying logistic regression (OR -O. O22, p-value = .440). Early age of menarche was obtained as a risk factor independent of others (OR-10.448, p-value = 0.00). While analyzing the regularity of the cycles, it was seen that irregular cycles were a risk factor for the development of adnexal masses (OR-3.806, p-value = 0.001). **Conclusion:** Early age of menarche was found to increase the risk of adnexal masses 10 fold. Irregular cycles were also found to be a risk factor. While analyzing the protective factors, oral contraceptive use and dysmenorrhea were found to be protective. The idea of these risk factors will help in early screening and management of patients with adnexal masses, out of which a small proportion will be malignant masses.

Keywords: Oral Contraceptive Use, Dysmenorrhea, Early Age of Menarche, Irregular Cycles.

INTRODUCTION

The term adnexa is derived from the pleural form of the Latin word adnexus, which means appendage. The adnexa of the uterus includes the ovaries, fallopian tubes, and the structures of the broad ligament. Adnexal masses refer to the ovarian masses or cysts; tubal/para tubal cysts, hydrosalpinx, and other non-ovarian causes like endometrioma, pelvic inflammatory disease, tubo-ovarian abscess, ectopic pregnancy, and many other causes. An adnexal mass can be found in females of all ages with significantly variable prevalence. Adnexal masses are common among women of all age groups but more common among women of reproductive age. Adnexal mass may be of gynecological or non-gynecological origin. An adnexal mass may be benign or malignant. Epidemiology presumes that human diseases do not occur randomly and that there are causal and preventive factors that can be identified. There are multiple risk factors that can be identified associated with the development of adnexal masses. With the increasing prevalence of adnexal masses, it is important to understand the epidemiological factors causing these masses, and it will be helpful in the screening, early detection, and management.

AIMS AND OBJECTIVES

- To study risk factors for adnexal masses in females less than 45 years.
- To study the distribution of different types of adnexal masses in the study population.
- Identification of risk factors of benign and malignant ovarian tumors andendometriosis.

MATERIALS & METHODS

This was a hospital-based case control study conducted among 135 females of age less than 45

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years who presented with sonographic evidence of adnexal masses to the Department of Obstetrics and Gynecology at SAT Hospital, Trivandrum, a government institution, after obtaining clearance from the institutional ethics committee and written informed consent from the study participants.

Inclusion Criteria

- All females less than 45 years of age attending outpatient department with a scan showing adnexal masses.

Exclusion Criteria

- All patients who are pregnant
- Non-gynecological causes of adnexal masses
- Patients presenting with an adnexal mass associated with some congenital anomalies
- Patients with a functional cyst or corpus luteal cyst since that would regress on its own
- Patients who are not willing to participate in the study.

Statistical Methods

Analysis of data was done using appropriate statistical software, SPSS version 26.

RESULTS

Age	Benign Ovarian Mass		Malignant Ovarian Mass		Endometriotic Mass		PID Mass	
	No	%	No	%	No	%	No	%
15-20	6	10	0	0	1	3.1	0	0
21-25	11	18.3	0	0	1	3.1	0	0
26-30	12	20.0	1	4.0	3	9.4	3	60.0
31-35	9	15.0	2	8.0	2	6.3	2	40.0
36-40	9	15.0	3	12.0	9	28.1	0	0
41-45	13	21.7	19	66.0	16	50.0	0	0

Distribution of Different Adnexal Masses in Age Group

Age of Menarche	Controls		Cases		Chi Square	P-Value	OR
	no	%	no	%			
>13	113	83.7	49	36.3	63.2	0.000	9.00
<13	22	16.3	86	63.7			

Comparison of Cases and Controls with Age of Menarche Before and After 13 Years

Age of Menarche	Benign Ovarian Mass		Malignant Ovarian Mass		EndometrioticMass		PID Mass	
	no	%	no	%	no	%	no	%
<13	34	56.7	17	68.0	23	71.9	4	80
>13	26	43.3	8	32	9	28.1	1	20

Distribution of Different Adnexal Masses with Age of Menarche

Table 1

According to the distribution of various adnexal masses studied, benign ovarian mass is most common in the age group 41 to 45 (21.7%), followed by the age group 36 to 40.

Malignant ovarian mass incidence highly increased as the age advanced. Most distribution of malignant mass found in age group of 41-45, which was 66% (chi square = 66.1 df = 18 p = .000).

A significant relation was obtained between the age of menarche and adnexal masses. According to the results obtained, menarche before 13 years is a risk factor for adnexal masses. The odds of development of adnexal masses in the early menarche group were 9 (OR - 9.00, p-value = 0.00).

Cases with different adnexal masses and ages of menarche were compared. Among cases with malignant ovarian mass, 68% had menarche before 13 years, which was found to be significant. Benign ovarian mass 56.7% and endometriotic mass 71.9% (Chi square = 2.9, p = 3.93, p = 3.93).

	Group				Chi Square	P-Value
Cycles	Controls		Cases			
Regular	113	83.7%	87	64.4%	**13.0**	**0.00**
Irregular	22	16.3%	48	35.6%		

Regularity of Cycles in Cases and Controls

History of Dysmenorrhea	Group					
	Control		Case			
	No	%	No	%	Chi Square	P Value
Yes	28	20.7	63	46.7	20.3	0.000
No	107	79.3	72	53.3		
Total	135	100.0	135	100.0		

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History of Dysmenorrhea in Cases and Controls						
	Controls		**Cases**		**Chi Square**	**P-Value**
	No	**%**	**No**	**%**		
15-19	14	12.7	9	9.1	19.9	0.001
20-24	65	59.1	35	35.4		
25-29	22	20.0	33	33.3		
30-34	8	7.3	18	18.2		
35-39	1	0.9	4	4.0		
total	110	100.0	99	100.0		

Age of First Child-Birth in Cases and Controls						
	Controls		**Cases**		**Chi Square**	**P-Value**
	No.	**%**	**No.**	**%**		
yes	43	31.9	24	17.8	7.2	0.007
no	92	66.1	111	82.2		

History of Oral Contraceptive Use in Cases and Controls

Table 2

According to Figo, menstrual cycles are considered normal if the frequency of cycles is between 24 and 38 days, with a variation of 2-20 days.

Among the study population with adnexal masses and without masses, it was found that cases had more irregular cycles (35.6%) while compared to controls (16.3%) (chi square – 13.0, df-1 p-value = 0.00). A significant association was seen between those cases with irregular cycles and adnexal masses. Odds of developing adnexal masses in a population with irregular cycles were 3 times (OR-3.806).

From the study, it was noted that those patients with adnexal masses had 46.7% history of dysmenorrhea, while controls had only 20.7% history of dysmenorrhea. According to the analysis done, a significant relationship was found between the history of dysmenorrhea and adnexal masses. (OR- 0.004).

Distribution according to age of first childbirth is given. In the control group, age groups 20–24 had a maximum population of 59.1%, and in cases, this group had 35.4%. The number of cases with early first childbirth is less while compared to the control group. According to analysis, there is a significant association between age at first childbirth and adnexal masses. (OR-0.910) History of oral contraceptive use among patients with adnexal masses and controls were compared; it was found out that among cases oral contraceptive intake was 17.8% and among controls intake was around 31.9%. Significant association was found between history of oral contraceptive intake and risk for adnexal masses. (OR-0.230)

OCP use	**Type of Mass**					
	Benign Ovarian Mass		**Malignant Ovarian Mass**		**Endometriotic Mass**	
	No	**%**	**No**	**%**	**No**	**%**
Yes	8	13.3	0	0.0	14	43.8
No	52	86.7	25	100.0	18	56.3
Total	60	100.0	25	100.0	32	100.0

OCP Use in Various Adnexal Masses						
	Controls		**Cases**		**Chi Square**	**P-Value**
	No.	**%**	**No.**	**%**	13.4	0.00
Yes	56	41.5	86	63.7		
No	79	58.5	49	36.3		

History of Active or Passive Smoking in Cases and Controls							
	Controls		**Cases**		**Chi Square**	**P-Value**	**OR**
	No.	**%**	**No.**	**%**	12.9	0.00	5.3
Yes	5	3.7	23	17			
No	130	96.3	112	83.0			

Family History of Endometriosis in Cases and Controls							
	Controls		**Cases**		**Chi-Square**	**P-Value**	**OR**
	No.	**%**	**No.**	**%**	12.8	0.000	3.3
Yes	14	10.4	37	27.4			
No	121	89.6	98	72.6			

History of Infertility in Cases and Controls

Table 3

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It was found that among patients with malignant ovarian mass, none of them ever used any kind of oral contraceptive pills. (Chi square = 20.0 df = 2 p = .000)
The histories of active and passive smoking in cases and controls were compared, and it was seen that in cases 63.7% had smoking exposure, whereas in controls only 41.5% had smoking exposure. A significant relationship was found between the history of smoking exposure and the development of adnexal masses. (OR-0.711)
Among cases, 17% had a positive family history of endometriosis, whereas only 3.7% of controls had a positive family history of endometriosis. There was a significant relationship found between family history of endometriosis and occurrence of adnexal masses. Family history of endometriosis increases the risk of adnexal masses by 5 times.
While comparing the history of infertility between cases and controls. It was found that among cases 27.4% had a history of infertility, whereas in controls only 10.4% had a history of infertility. There was a significant association between the history of infertility and the occurrence of adnexal masses. History of infertility increases the risk of adnexal masses by 3 times.

History ofInfertility	Type of Mass							
	Benign Ovarian Mass		Malignant Ovarian Mass		Endometriotic Mass		PID Mass	
	No	%	No	%	No	%	No	%
Yes	10	16.7	7	28.0	18	56.3	1	20.0
No	50	83.3	18	72.0	14	43.8	4	80.0
Total	60	100.0	25	100.0	32	100.0	5	100.0

History of Infertility in Different Adnexal Masses

	Controls		Cases		Chi Square	P-Value	OR
	No.	%	No	%			
Yes	7	5.2	21	15.6	7.8	0.05	3.4
No	128	94.8	114	84.4			

History of Ovulation Induction in Cases and Controls

Table 4

The history of infertility varied among patients with different adnexal masses. Among patients with endometriotic cyst, 56.3% had a history of infertility. (Chi square = 16.0 df = 3 p = .001)
The history of ovulation induction was positive in 15.6% of cases and 5.2% of controls. There was a significant relationship between history of ovulation induction and adnexal masses. History of ovulation induction increases the risk of adnexal masses by 3 times.

	B	S.E.	Wald	df	Sig.	Exp (B)
Age of First Child Birth	-.094	.380	.061	1	.804	.910
Gravida	.385	.477	.650	1	.420	1.469
Age of Menarche	2.346	.364	41.525	1	.000	10.448
H/O Ovulation Induction	-1.097	.595	3.395	1	.065	.334
History of Infertility	-.601	.483	1.545	1	.214	.548
Family History of Endometriosis	-.953	.617	2.385	1	.122	.385
Family History of Malignancy	-.588	.390	2.280	1	.131	.555
h/o Smoking	-.341	.346	.971	1	.324	.711
OCP Use	-1.470	.417	12.457	1	.000	.230
h/o Tubal Ligation	-.823	.481	2.924	1	.087	.439
H/o Dysmenorrhea	-.821	.358	5.262	1	.022	.440
h/o Intermenstrual Bleeding	-.186	.444	.176	1	.675	.830
Cycles	1.337	.386	11.980	1	.001	3.806
Constant	2.978	1.053	7.995	1	.005	19.644

Table 5: Logistic Regression

Variables with significant p-values were used for logistic regression. Age of first child birth, gravida, age of menarche, H/O ovulation induction, history of infertility, family history of endometriosis, history of smoking, oral contraceptive use, history of tubal ligation, history of dysmenorrhea, history of intermenstrual bleeding, and regularity of the cycles were included. Age of menarche was obtained as a risk factor independent of others (OR-10.448, p value-0.000).
Other risk factors obtained were irregular cycles (OR = 3.806, p-value = 0.001). While analyzing, it was

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found that OCP use was a protective factor. OR = 0.230, p-value = 0.022). A history of dysmenorrhea was also found to be a protective factor. (OR = 0.022, p value = 0.440)

DISCUSSION

Type of Mass

After menarche, adnexal masses are mostly likely to be follicular and corpus luteum cysts of the ovary. The majority of the masses in this age group will be benign cysts of ovarian origin.[1]

Another study conducted in 2015 showed that adenexal masses were more common than ovarian malignancies.[2] In the prostate, lung, and colon ovarian cancer screening trial, the simple adnexal cyst detected among 16,000 women was 14%.

In the study conducted, out of the total masses, the majority of masses were benign ovarian masses (44.4%), followed by endometriotic cysts, which were around 23.7%. Malignant ovarian masses were 18.5%, paraovarian masses were 9.6%, and adnexal masses, which may be due to pelvic inflammatory disease, were the least, which was around 3.7%.

Association with Age

Adnexal masses can be found in all age groups, ranging from fetuses to old age. Different types of adnexal masses show peak at different age populations. Murthy et al., reported that ovarian tumors increase from 35 years of age and reaches peak between 55 and 64 years.[3] In the study, it was seen that there is a steady increase in the number of cases after 40 years of age; most of the malignant ovarian masses were in this group, which agreed with the findings of Mondal et al., who found most of the malignant tumors above 40 years of age.[4] Benign ovarian mass and malignant ovarian mass had the highest incidence above 40 years, which was 21.7% and 66%, respectively.

Association with BMI

The majority of the patients had a normal BMI (37%), followed by overweight (34%). No particular association was found with BMI and the development of adnexal masses.

Association with Menstrual Factors

Parazzini et al., studied the influence of various menstrual factors on the risk of ovarian tumors.[5] They reported that the risk increased with early menarche and later age of menopause. This increases risk by increasing the number of ovulatory cycles according to the incessant ovulation hypothesis.[6] Conversely, a late age at menopause reduces the risk as per the gonadotropin hypothesis. According to this hypothesis, the bigger concentrations of FSH and LH that accompany ovarian senescence increase the risk of developing ovarian cancer. This theory says that early age at menopause may be more directly linked to early onset of ovarian cancer (under 45 or 50 years) than later onset disease.[7]

In this study, while comparing cases and controls, most of the cases had an early menarche while compared to the control group. 63.7% of cases had menarche before 13 years, compared to cases, which were only 16.3%. This is in accordance with the theory of incessant ovulation.

The age of menarche and distribution among the patients with various adnexal masses were taken into consideration. It was found that the age of menarche was less than 13 years in 56.7% of patients with benign ovarian mass, 68% with malignant ovarian mass, 71.9% with endometriotic cysts, and 80% of patients with PID. Hence there is a significant relation between the early age of menarche and the development of adnexal masses.

While comparing the study group, a significant association was found between regularity of cycle and adnexal masses. Patients with adnexal masses had more irregular cycles (35.6%) when compared with that of controls. Studies show inconclusive findings and show both increased and reduced risk associated with irregular cycles and also null associations. Piera et al., reported a higher risk of ovarian carcinoma in women with irregular cycles, with 13% of the cases showing irregular cycles in their study. This may be explained by the chronic unopposed estrogen action in those who present with irregular cycles for longer duration. Studies on endometriosis prove that shorter cycle length, often defined as <27 days, increases the risk of endometriosis.[8]

The pattern of intermentrual bleeding was compared. In this study, 23% of cases had a history of intermenstrual bleeding, while only 11% of controls had intermenstrual bleeding.

Association with Marital and Obstretric Factors

According to the third national cancer survey, there is no available data regarding the relationship between marital status of the women and ovarian masses. Stewart et al.,[9] and Joly et al.,[10] estimated that married women who had been pregnant at least once had half the ovarian tumor risk than those who had never been pregnant. Graham[11] found out that the frequency of nulliparity among patients with ovarian cancers is as high as that with endometrial and breast cancer. In this study, among cases were 83% married and 17% were unmarried, while among controls were 84% married and 16% unmarried. No significance was found between marital status and risk for the development of adnexal masses.

Uninterrupted ovulation and excessive exposure to gonadotropins are thought to play a major role in the development of ovarian masses. Pregnancy reduces the risk by suspending ovulation and inhibiting the synthesis of gonadotropins. Moreover, pregnancy increases the level of estrogen and progesterone; the increased progesterone levels may prevent adnexal masses by inhibiting proliferation of ovarian epithelium, thereby accelerating cellular

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differentiation and promoting apoptosis. Thus, as per Ali-Yavuczan et al., as parity increases, the risk decreases.[12] The incessant ovulation hypothesis is also in accordance with the fact that an increase in parity protects against ovarian mass formation. Women with endometriosis have a well-documented risk for infertility, but endometriosis as a cause for infertility is controversial [Kennedy et al.]. In this study, no significant relation was seen between parity and the development of adnexal masses. Among the cases, 26.7% were nulliparous, and among controls, 18.5% were nulliparous. Patients with parity >2 are found only in 31.7% with benign ovarian mass, 60% with malignant ovarian mass, and 37.5% with endomertiotic cyst.

Association with Tubal Ligation

Several systematic reviews and meta-analyses of studies available documented a significant reduction of ovarian tumor risk in women who had undergone tubal ligation. The significant protective effect was shown even in a subgroup of women after 10–14 years since tubal ligation. Koch et al., reported an insignificantly increased relative risk of ovarian cancer in women after tubal ligation. In this study, no significant association was found between the history of tubal ligation and the development of other adnexal masses. Here, 68.3% of benign ovarian mass patients and 48% of malignant ovarian mass patients had not undergone tubal ligation.

Association with Oral Contraceptive Use

La Vecchia et al., found that ever use of any hormonal contraceptives reduced the risk of ovarian cancer by approximately 30%, and a steady inverse relation is observed with the duration of use, with a decrease in the relative risk of about 5% per year of use. Thus, the protection was about 50% for long-term use of 10 years or more.[13] Similar findings were reported by Liva Iversen et al., with a stronger association with longer periods of current OCP use.[14]

In this study, among controls and cases, the use of oral contraceptives was studied; the duration of use was not studied separately. Among controls, 31.9% had a history of oral contraceptive use, whereas in cases, 17.8% only had a history of oral contraceptive use. Thus, comparing them statistically, oral contraceptives can be considered as a protective factor in the development of adnexal masses, which was in accordance with many other previous studies. Considering the individual adnexal masses, 86.7% of patients with benign ovarian mass, 100% of patients with malignant ovarian mass, and 56.3% with endometritic mass don't have a history of oral contraceptive intake.

Association with Smoking and Substance Abuse

In this study, history of active or passive smoking was taken into consideration; among cases, 63.7% and controls, 41.5%, had histories of smoking exposure. A significant association was found between smoking and the development of adnexal masses. 75% of patients with benign ovarian mass, 68% with malignant ovarian mass, 60% with benign ovarian mass, and 40% with PID mass had a history of smoking exposure. In cases 23.7% had a history of substance abuse, whereas in controls 15.6% had a history of substance abuse.

Association with Family History of Malignancy and Endometriosis

Several studies have reported an association between family history of malignancy and ovarian cancer. Familial ovarian cancer is described by the occurrence of disease in first- or second-degree relatives affected by ovarian cancer. Lynch et al. reported the same in their studies. It is estimated that approximately 5–10% of ovarian cancers can be due to hereditary factors. Three hereditary syndromes in which familial aggregation of ovarian cancer has been described: site-specific ovarian cancer syndrome, breast ovarian cancer syndrome, and hereditary non-polyposis colorectal cancer. In this study, family history of all types of malignancies was taken into account. Among cases, 39.3% had a family history of malignancies, and in controls, 24.4% had a family history of malignancies. 50% of patients with endometriotic mass and 48% with malignant ovarian mass had family history of malignancies. No significant association was found.

Association with Past History

Several histories from the past were taken into account. While comparing the history of infertility between cases and controls. It was found that among cases 27.4% had a history of infertility, whereas in controls only 10.4% had a history of infertility. There was a significant association between the history of infertility and the occurrence of adnexal masses. History of infertility increases the risk of adnexal masses by 3 times. Several studies have shown that history of endometriosis and ovarian tumors can lead to infertility.

While studying the infertility, the history of ovulation induction was also taken into consideration. The history of ovulation induction was positive in 15.6% of cases and 5.2% of controls. There was a significant relationship between history of ovulation induction and adnexal masses. History of ovulation induction increases the risk of adnexal masses by 3 times.

History of STD or PID doesn't seem to have any significant effect on the development of adnexal masses.

Association with Diet

In this study, 47.4% of controls and 43.7% of cases had a high-fat diet. Among cases and controls, it was found that 84.4% of controls and 85.2% of cases were vegetarians. No significant association was obtained between dietary patterns and the development of

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adnexal masses.

CONCLUSION

We conducted a case-control study in the hospital comparing the risk factors of adnexal masses in young females less than 45 years. 135 cases were compared with 135 controls. Out of the 135 cases studied, 44.4% of cases were benign ovarian masses, 23.7% of cases were with endometriotic cysts, malignant ovarian masses were 18.5%, paraovarian masses were 9.6%, and adnexal masses due to pelvic inflammatory disease were 3.7%. Even though ovarian tumors are rare in this group, proper analysis of adnexal masses should be done to rule out malignancy. Increased incidence of malignancy in females of the study group (less than 45 years) was seen after 40 years of age. Risk factors associated with each adnexal mass were compared. Early age at menarche was observed to be a risk actor to the development of adnexal masses. Other risk factors obtained were irregular cycles. While analyzing, it was found that OCP use was a protective factor. A history of dysmenorrhea was also found to be a protective factor. Some of the modifiable risk factors were also found to be significant, like history of smoking, oral contraceptive use, and history of tubal ligation. Knowledge of these risk factors helps in the early identification of an adnexal mass and early treatment initiation. Identification of modifiable risk factors and counseling of patients can be helpful.

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