Effects of menarche,parity,primiparous age,and reproductive diseases on uterine fibroids of rural women in China

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Abstract

Objectives With the increasing prevalence of hysteromyoma among Chinese rural women at childbearing age, it has become a priority to identify the risk factors that predispose to corporeity and promote early prevention. The aim of the study is to explore the relationship between menarche age, female reproductive health and uterine fibroids.

Methods Study participants included 2,200 rural women of reproductive age who were screened for a cross-sectional study in the Anhui province. Data collected by questionnaire survey, gynecological and laboratory examinations were analyzed by Univariate and multivariate analysis to evaluate the risk factors for uterine fibroids.

Results Of the 2,200 women, 440 had uterine fibroids. In general, women with endometriosis, ovarian cysts and early menarche were more likely to suffer from hysteromyoma. Factors including more parity, appropriate late primiparous age and normal menstrual cycle were protective of uterine fibroids.

Conclusions Our findings indicate that a variety of modifiable factors may increase the risk of uterine fibroids and that relevant health departments should develop effective prevention and intervention measures to improve the reproductive health of rural women.

Introduction

Uterine fibroids originate from muscle cells in the uterus, and are often initially diagnosed as small nodules and polyps. With fibroids growing, some of them can even swell the lower abdomen. Leiomyoma or uterine fibroid tumor, the most common female pelvic benign tumor is classified based on its location relative to the layers of the uterus (as subserous, intramural or submucosa), occurring with an estimated incidence of 20% –40% in women during their reproductive age^{1,2}. Incidence of uterine leiomyoma varies with race and age³. Uterine leiomyoma is steroid dependent⁴. Because of the influence of estrogens and progestogens⁵, leiomyoma rarely occurs earlier than menarche and scarcely later than menopause. Women with uterine leiomyoma may have increased menstruation, prolonged menstruation, and lower abdominal pain during menstruation. However, the clinical manifestations of most patients are hidden or even no clinical manifestations⁶, which causes many women of childbearing age to miss the best treatment period, and most of them have to be treated by surgery. Most patients with late detection of uterine leiomyoma need to undergo hysterectomy, which is also the main reason why women are hospitalized for gynecological diseases^{7,8}. Study has supported that the earlier girls with menarche, the more likely they are to have uterine fibroids⁹. Early age of menarche is also reported to be relevant to complications such as type 2 diabetes, angiocardopathy, metabolic diseases^{10,11}, and cancer¹². The age of menarche can be influenced by genetic and environmental factors during childhood¹³, thereby supporting the “developmental origins of health and disease” hypothesis.

Exploring the relationship between age of menarche, parity, female reproductive diseases and hysteromyoma is of remarkable clinical and public health importance, especially in the context of declining age of menarche and increasing prevalence of hysteromyoma. This study is a population-based study of rural women of reproductive age in Anhui province.

Material And Methods

Setting and sample

This large cohort cross-sectional study was conducted between August 2005 and November 2007 in Anhui province, which is located in the east-central part of China covering an area of 39600km² and with a population of more than 70 million. At that time, more than 50% of the population lived in rural areas of the province; 17 million women were at child-bearing age, and nearly 80% of them were married.

This survey was designed by the Population and Family Planning Commission of Anhui Province and performed by Department of Public Health of Anhui Medical University. All workers gave informed consent and the study was approved by the Anhui Science and Technology Department and the Research Ethics Committee of Anhui Medical University. The selection of participants was carried out by a multistage stratification process as described previously.

Firstly, Anhui province was stratified based on administrative region and diverse landforms. Subsequently, several towns were picked out randomly within the stratification. Secondly in marking the town family planning service stations as the center, administrative villages randomly were selected within a 5 km radius from the center. Finally, qualified women from these administrative villages were investigated and women who could not recall with certainty their age at first menstruation were excluded to minimize bias in the outcome. A total of 53652 women were interviewed, of which 52874 responded to the questionnaires. Due to the large size of the original database, 2,200 women of reproductive age were randomly separated from the database after deleting the samples that were not consistent with the research topic.

Questionnaire, disease diagnosis, and data collection and classification

Questionnaires were handed to the interviewees by the staff to obtain specific study related information, which principally included sociodemographic characteristics, menstrual history, obstetrical history, health history, health care seeking behavior and so on. Prior to the start of the study, investigators were given permission to visit participants' home and maintain record of their home address to ensure high quality accuracy and completeness of the database. Information of women who arrived at the family planning service outlet of the villages was recorded. Residents who failed to show up were visited by investigators. Detailed information on the questionnaire survey is available in our previous articles¹⁴.

Gynecologists, laboratory technicians, and health workers obtain female reproductive health status through gynecological examination, laboratory testing. Initially, subjects were interviewed to gather information regarding past gynecological history, abnormal symptoms in pudendum, discomfort or pain in hypogastrium or other signs. After that vaginal excretion or cervical sample were taken with vaginal speculum, and blood samples were collected separately from each participant in a disinfected room for the diagnosis of RTIs (Reproductive Tract Infection). Gynecologists used ultrasound scanners to diagnose uterine fibroids in the participants.

Considering that most interviewees were born before the 1990s, the weak economy and the availability of fewer material resources in rural Anhui, we divided menarche into 3 groups based on age of onset: ≤ 12 , 13~16(Ref. group), ≥ 17 years. Primiparous age was also divided into three groups: ≤ 20 , 21~25(Ref. group), ≥ 26 years. The same grouping is done in parity: 0~1, 2~3(Ref. group), ≥ 4 children. According to the severity of symptoms, dysmenorrhea was divided into three groups: no (Ref. group), mild, and severe. Most of the remaining dichotomous data were naturally divided into two groups: non-exposed group (no = 0) and exposed group (yes = 1).

Statistical analysis

Two students utilized EpiData3.1 [EpiData Foreningen (EpiData Association), Odense, Denmark] to enter data and SPSS23.0 to analyze data separately. Univariate analysis was applied to calculate the odds ratio (OR) and 95% confidence interval (95%CI) to evaluate the relationship between diverse variables and incidence of uterine fibrosis. A multivariate stepwise logistic regression analysis was used to assess the net association between factors (including demographic characteristics, physiological characteristics, reproductive diseases) and hysteromyoma.

To minimize the effect of interference, dependent variables were controlled, as much as possible, in each multivariate stepwise logistic regression analysis. A value of $p < 0.05$ and 95% CI of OR that did not span zero was considered statistically significant.

Results

Various characteristics

Of the 2,200 women, 440 had uterine fibroids. The incidence of uterine fibroids was 20%. The sociodemographic characteristics, female physiology characteristic, and reproductive diseases are shown in Table 1-3. The average age of the 2,200 rural women of child-bearing age was 39.54 ± 5.96 years. Of the four age groups, the third group (36~45 years old) had the highest proportion (64.7%) of women. 99.5% of them were from Han nationality, and the rest were of ethnic minorities. 1,569 (73.1%) were below the primary school level in

education. Nearly half of them (45.5%) never attended school (not been listed). Most people have stable marriages (97.5%), the rest 2.5% including divorce, widowhood, remarriage, and so on. 54% of them earned less than 10000 RMB.

About two-thirds (70.4%) of women have their menarche at the age of 13~16, 11% before 12 years old. 1855(84.3%) of them had 2~3 children. 847 women had a history of abortion or induced labor. 1472(66.9%) people had their first child at the age of 21~25, 415(18.9%) before 20.

731(33.2%) women had vaginitis, 11.4% with pelvic inflammatory disease, and 41% with dysmenorrhea. More details about the various characteristics of women were presented in Table 1~3.

The distribution of uterine fibroids among diverse variables

Based on demographics, there was no statistical difference in the frequency distribution of uterine leiomyoma in groupings based on nationality, occupation and yearly family income, but statistical differences were found in the distribution based on women's age, education and marital status ($p < 0.05$). Based on physiological characteristics, there was no statistical difference in the frequency distribution of uterine leiomyoma based on the history of abortion, but significant differences were found in the distribution based on menarche, parity and primiparous age ($p < 0.001$). With regard to female reproductive diseases, there were significant differences found in the distribution of uterine leiomyoma based on a history of vaginitis, pelvic inflammation, endometriosis, ovarian cyst and menstrual disorders ($p < 0.001$), only except the dysmenorrhea. More information was provided in table 1 (Table1 is larger than A4 paper and is placed at the end of the text, before References).

Risk factors for uterine fibroids

Binary logistics regression analysis with the dependent variable of women with or without fibroids (no=0, Yes = 1) and independent variables of various characteristics presented that most demographics (nationality, occupation, education, marital status, family income),

except the women's age, were not associated with uterine leiomyomas (Table2). Compared to the second age group (26~34 years old), advanced age (age≥35 years old) was associated with an increased risk of leiomyomas.

Table2: Risk factors for uterine fibroids in sociological characteristics

Variables	Total sample n (%)	Uterine fibroids	
		n (%)	OR (95%CI)
women's age			
≤25	45(2%)	8(1.8%)	1.25(0.56-2.81)
26~35	442(20.1%)	65(14.8%)	Ref.
36~45	1424(64.7%)	300(68.2%)	1.55(1.16-2.07)
≥46	289(13.1%)	67(15.2%)	1.75(1.20-2.56)
Nationality			
Han nationality	2190(99.5%)	8(99.5%)	Ref.
Minority	10(0.5%)	2(0.5%)	1.0(0.21-4.73)
Occupation			
Farmer	2062(73.7%)	404(91.8%)	Ref.
Others ^a	138(6.3%)	36(8.2%)	1.45(0.98-2.15)
Education			
≤Primary school	1569(73.1%)	293(66.6%)	0.8(0.63-1.01)
Middle school	574(26.1%)	128(29.1%)	Ref.
High school	57(2.6%)	19(4.3%)	1.74(0.97-3.13)
Marital status			
Married	2144(97.5%)	435(98.9%)	Ref.
Unstable marriage status	56(2.5%)	5(1.1%)	0.39(0.15-1.03)
Early family income			
Less than 4999 RMB	398(18.1%)	79(15.8%)	0.80(0.59-1.09)
5000-9999 RMB	787(36.0%)	160(36.6%)	0.98(0.78-1.23)
More than 10,000 RMB	1004(45.9%)	208(47.6%)	Ref.

OR: odds ratio; CI: confidence interval.

Values(P<0.05) in bold mean they are statistically significant.

^aIncluding workers, businessmen, and waitress and so on.

Results in table3 suggested that AOM, parity, and primiparous age were significantly associated with uterine fibroids. People with early menarche (≤12, OR=1.57, 1.16-2.12) or

early primiparous age (≤ 20 , OR=1.3, 1.01-1.68) or less parity (0~1 child, OR=1.577, 1.05-2.37) may have a higher risk of leiomyomas. However, abortion or induced labor (95%CI: 0.78-1.20), pelvic inflammation (95%CI:0.79-1.51), and dysmenorrhea (no, Ref.; mild, 95%CI: 0.77-1.21; severe, 95%CI: 0.83-1.84) were not materially associated with the risk of uterine fibroids. The rest results of gynecological diseases detailed in table3 also shown that the factors independently associated with an increased risk of leiomyomas were vaginitis (OR=4.05, 3.26-5.04), endometriosis (OR=20.3, 7.70-53.5), ovarian cyst (OR=8.84, 4.72-16.53), and menstrual disorder (OR=9.17, 4.59-18.33). Detailed information from the data was given in table3.

Table3. Risk factors for uterine fibroids in female physiology characteristic and reproductive diseases.

Variables	Total sample n (%)	Uterine fibroid	
		n (%)	OR (95%CI)
Age of menarche			
≤12	243(11%)	71(16.1%)	1.57(1.16-2.12)
13~16	1549(70.4%)	323(73.4%)	Ref.
≥17	408(18.5%)	46(10.5%)	0.48(0.35-0.67)
Parity			
0~1	122(5.5%)	35(8%)	1.577(1.05-2.37)
2~3	1855(84.3%)	377(85.7%)	Ref.
≥4	223(10.2%)	28(6.3%)	0.56(0.37-0.85)
Abortion or induced labor			
No	1353(61.5%)	268(60.9%)	0.97(0.78-1.20)
Yes	847(38.5%)	172(39.1)	Ref.
Primiparous age			
≤20	415(18.9%)	102(23.2%)	1.3(1.01-1.68)
21~25	1472(66.9%)	295(67%)	Ref.
≥26	313(14.2%)	43(9.8%)	0.64(0.45-0.89)
Vaginitis			
No	1469(66.8%)	178(40.5%)	Ref.
Yes	731(33.2%)	262(59.5%)	4.05(3.26-5.04)
Pelvic inflammation			
No	1949(88.6%)	386(87.9%)	Ref.
Yes	250(11.4%)	53(12.1%)	1.089(0.79-1.51)
Endometriosis			
No	2170(98.7%)	415(94.5%)	Ref.
Yes	29(1.3%)	24(5.5%)	20.3(7.70-53.5)
Ovarian cyst			
No	2153(97.9%)	408(92.9%)	Ref.
Yes	46(2.1%)	31(7.1%)	8.84(4.72-16.53)
Menstrual disorder			
No	2161(98.3%)	413(94.1%)	Ref.
Yes	38(1.7%)	26(5.9%)	9.17(4.59-18.33)
Dysmenorrhea			
No	1300(59.0%)	259(58.8%)	Ref.
Mild	747(34.0%)	145(33%)	0.97(0.77-1.21)
Severe	153(7.0%)	36(8.2%)	1.24(0.83-1.84)

OR: odds ratio; CI: confidence interval.

Values(P<0.05) in bold mean they are statistically significant.

Discussion

Considering the basic national conditions, rural areas are poorer, less informed and have less access to family planning services than cities, as a result, rural women are at a higher risk of gynecological diseases. Although the fertility rate of rural women in Anhui province is high, prevention of gynecological diseases is still insufficient.

The influence of uterine fibroids on the female population is of great significance no matter from the social, economic or medical point of view. Fibroids in different locations of the uterus with different incidence, generally speaking, intramural fibroids are the most common, followed by sub-serosal fibroids, and finally sub-mucosal. The degree of their damage to fertility also depended on their locations, inversely, among which sub-mucosal fibroids are the most harmful to fertility¹⁵. Related research have confirmed that sub-mucosal fibroids have the lowest incidence, located beneath the endometrium, which more likely lead to irregular bleeding and adverse reproductive effects in women^{16,17} and prior studies have illustrated that infertility is also associated with uterine fibroids^{9,18}, especially at earlier ages¹⁹. Although women with uterine fibroids often have irregular uterine bleeding²⁰, the specific cause has not been identified. Hypothesis thought it may be caused by uterine fibroids pressing on the endometrial venous plexus. Our result, 20% prevalence rate in 2200 cases, is in line with available data^{1,2} which confirmed that fibroids are the most common pelvic tumor with an estimated incidence of 20% –40% in women during their child-bearing age. The prevalence of uterine fibroids is also age dependent. For example, in Germany prevalence of uterine fibroids increased from 21.3% (30–35 years old) to 62.8% (46–50 years old) and subsequently declined from 56.1% to 29.4% in women between 51 and over 55 years of age²¹. In fact, it is equivalent to the effect of estrogen because the secretion of estrogen varies in different age groups. Our research indicated that highest prevalence (68.2%) of fibroids groups was found among people aged 36~45 years (OR = 1.55, 95%CI: 1.06–2.07), lower prevalence (16.6%) among people aged <35 years, and the least morbidity (15.2%) among women aged ≥46 years. The highest prevalence appeared in age groups of 36~45 years were in agreement with previous study conducted elsewhere²², which also illustrated that uterine fibroid is very common among women in their 30s to 40s and age is a risk factor for uterine fibroids^{22,23}. Uterine fibroids are estrogen-dependent, so decreased hormone levels in menopausal women may also explain the least prevalence (15.2%) of fibroids age group (≥46 years old).

From a genetic point of view, some studies have suggested an association between the age of menarche and chromosomes 6 and 9²⁴. For a long time, genetic underpinnings of uterine fibroids were largely ignored by the scientific community. However, recent reports have proved that cytogenetics play an important role in the pathogenesis of fibroids. The TC227 allele of HMGA2 was shown to be involved in the regulation of tumor tumorigenesis and development²⁵. A study on the histone analysis of fibroids demonstrated that overexpression of extracellular matrix, and estrogen and progesterone receptors are related to signal transduction pathways in the pathophysiology of fibroids²⁶. Physiologically, menstruation is the periodic shedding of the endometrium influenced by various hormones; factors affecting the secretion of related hormones affect menstruation. Early menarche occurs due to higher estrogen levels²⁷. In another word, early age of menarche is equivalent to early start of ovulation, and early exposure to estrogen and progesterone²⁸, which could explain our results that early menarche age (≤12years, OR = 1.57, 95%CI: 1.16–2.12) is an adverse factor for fibroids. In summary, our study is quite consistent with previous reports on the relationship between the age of menarche and the prevalence of

uterine fibroids^{9,29}. These reports collectively indicated that the earlier the age of menarche, the higher the rate of fibroids²⁹.

Agreed with prior studies, just as shown in table3, the number of births is a protective factor for uterine fibroids. With the decrease in parity (0~1 child, OR = 1.577, 95%CI: 1.05–2.37), the prevalence of uterine fibroids is increasing^{19,30}. One hypothesis suggests that the protective effect of pregnancy on fibroids occurs during postpartum uterine involution, which is actually more like uterine remodeling. The process includes high levels of apoptosis and contraction of muscle cells for regaining uterine size. Uterine remodeling can enhance the selective elimination of abnormal cells that have transformed during apoptosis. In other words, postpartum uterine regurgitation can eliminate abnormal tumor cells³¹. Another reason being temporary cessation of menstruation during pregnancy leads to less exposure to estrogen and progesterone.

As ovarian cancer and endometriosis share common genetic alterations, such as PTEN, p53, and bcl gene mutations, it is naturally inferred that malignant gene transition exists between them³². Women with symptomatic leiomyoma have a higher risk of endometriosis³³, nevertheless, our results suggested that endometriosis is a risk factor(OR = 20.3, 95%CI: 7.7–53.5) for uterine fibroids, which reflected mutual causality.

Earlier study has observed women with incident fibroids, those with a previous BV diagnosis are more likely to have 2 or more fibroids compared with 1 fibroid³⁴. This is consistent with our study that found a positive association between vaginitis (OR = 4.05, 95%CI: 3.26–5.04) and the risk of developing uterine leiomyomas.

The symptoms of genital tract infection are usually ignored by women as they are not obvious, but long-term infection can stimulate bulking of the endometrium resulting in uterine fibroids³⁵, which can has a capacity for increasing the risk of uterine fibroids³⁶.

Early primiparous age (≤ 20 , OR = 1.3, 95%CI:1.01–1.68) has been associated with a significant increase the prevalence of uterine fibroids from table 3. According to the information from encyclopedia of Chinese women, medicine health care voucher: people's endocrine systems will mature around the age of 23, when their ovaries can release the highest quality ootid and the optimal reproductive age for women is 24~29 years old; Physiologically, due to the immaturity of the multiple systems in body,too early primiparous age will increase the risk of gynecological diseases and cervical cancer in the future. Therefore, we think our result is in line with clinical significance.

Shown in our study, both ovarian cysts (OR = 8.84, 95%CI: 4.72–16.53) and menstrual disorders (OR = 9.17, 95%CI: 4.59–18.33) have adverse effects on the prevalence of uterine fibroids. The ovary is a gonad organ whose main function is to produce ootid and secrete various gonadal hormone. Ovarian cysts will give rise to abnormal secretion of the hormone that can induce uterine fibroids. Noriko Kato and Tadashi Hayasaka identified ovarian tumors with functioning stroma is positively correlated with the increase of

serum estrogen level³⁷. The reasons for irregular menstruation vary and can arise due to diverse conditions ranging from hormone disorder, malignant tumor, reproductive tract infection, to the use of certain medications and so on. Furthermore, [Jiao Jiao](#) and [Matthew Sagnelli](#) have ascertained that an array of abnormally expressed genes present in patients with menstrual disorders also appeared in the signaling pathways of oncogenesis³⁸.

Conclusion

In brief, our data indicates that female reproductive diseases and earlier menarche are risk factors for uterine fibroids, while multiple parity provides protection from uterine fibroids. Therefore, in order to reduce the prevalence of female uterine fibroids and improve the reproductive health index, it is necessary to prevent the above risk factors in advance.

Limitations

List of risk factors known to increase the occurrence of uterine fibroids have been listed in numerous articles, which are more comprehensive compared to our study results. This is mainly because the applicable sample size provided in our paper is small after deleting incomplete or inconsistent data. In addition, due to limited financial and human resources, we did not make a detailed classification of uterine fibroids and counted the number of uterine fibroids per patient. Differences in the clinical experience of ultrasound technicians may have prevented some women whose intrauterine fibroids are small from being detected.

Declarations

Conflict of interest

All authors declare no conflict of interest.

Authors' contributions

Author Bing-Jie Wu designed the study, performed the statistical analysis, wrote the protocol and the first draft of the manuscript. Bing-Jie Wu, Fei Zhong, Xiu-Jun Zhang and Cheng-Yang Hu helped to design the work and interpreted data, revised the contents of the manuscript which were inappropriately expressed. Chun-Yan Shao, Yun Zhu, Kai Huang and Wu Wei all participated in the data collation. All authors read approved the final version of the article.

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Ethical compliance

All the research procedures referring to interviewees which were scrupulously designed and implemented in the study conformed to moral standards of the Anhui Science and Technology Department and the Research Ethics Committee of Anhui Medical University in June 2006 (#060230060).

Informed consent

Every participant involved in the research gave informed consent.

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Availability of data and material

The corresponding author can provide the applicable data or material if the article requires.

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Table

Table1: Multiple characteristics of 2,200 women and the distribution of uterine fibroids among variables

Variables	Women without uterine fibroids	Women with uterine fibroids	P-value	
	n (%)	n (%)		
Women's age			10.73	0.013<0.5
≤25	37(82.2%)	8(17.8%)		
26~35	377(85.3%)	65(14.7%)		
36~45	1124(78.9%)	300(21.1%)		
≥46	222(76.8%)	67(23.2%)		
Nationality			0.000	=1.0
Han nationality	1752 (80.0%)	438 (20.0%)		
Minority	8 (80.0%)	2 (20.0%)		
Occupation			3.410	0.065
Farmer	1658 (80.4%)	404 (19.6%)		
Others ^a	102(73.9%%)	36(26.1%%)		
Education			9.954	0.007<0.05
≤Primary school	1276(81.3%)	293(18.7%)		
Middle school	446(77.7%)	128(22.3%)		
▯Middle school	38(66.7%)	19(33.3%)		
Marital status			4.402	0.036<0.05
Married	1702 (79.7%)	432 (20.3%)		
Unstable marriage status	51▯91.1%▯	5▯8.9%▯		
Yearly family income			2.142	0.343
Less than 4999 RMB	329 (82.7%)	69 (17.3%)		
5000-9999 RMB	627 (79.7%)	160 (20.3%)		
More than 10,000 RMB	796 (79.3%)	208 (20.7%)		
Age of menarche ^b			33.02	<0.001
≤12	172(70.8%)	71(29.2%)		
13~16	1226(79.1%)	323(20.9%)		
≥17	362(88.7%)	46(11.3%)		
Parity ^b			13.60	0.001
0~1	87(71.3%)	35(28.7%)		
2~3	1478(79.7%)	377(20.3%)		
≥4	195(87.4%)	28(12.6%)		
Abortion or induced labor ^b	675 (79.7%)	172 (20.3%)	0.081	0.776
Primiparous age ^b			13.11	0.001
≤20	313(75.4%)	102(24.6%)		
21~25	1177(80%)	295(20%)		
≥26	270(86.3%)	43(13.7%)		
Vaginitis ^c	469(64.2%)	262(35.8%)	171.7	<0.001
Pelvic inflammation ^c	197(85.7%)	33(14.3%)	5.07	0.024<0.05

Endometriosis ^c	5 (17.2%)	24 (82.8%)	72.53	<0.001
Ovarian cyst ^c	15 (32.6%)	31 (67.4%)	66.14	<0.001
Menstrual disorder ^c	12 (31.6%)	26 (68.4%)	56.83	<0.001
Dysmenorrhea ^c			1.358	0.507
No	1041(80.1%)	259(19.9%)		
Mild	602(80.6%)	145(19.4%)		
Severe	117(80%)	36(23.5%)		

Values(P<0.05) in bold mean they are statistically significant.

^a Including workers, businessmen, and waitress and so on.

^b Belong to female physiology characteristic

^c Female reproductive diseases

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