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Idiopathic Granulomatous Mastitis and History of Hypothyroidism: Intervening Data of a Prospective Multicenter Trial and Meta-Analysis of the Existing Literature

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ABSTRACT

Background: Idiopathic granulomatous mastitis (IGM) is a rare benign breast disease that mostly occurs in reproductive ages in parous women. Hormonal, autoimmune, and microbial causes have been implicated as causes. We carried out this prospective study to investigate the reproductive factors and underlying disease states in IGM.

Methods: This study was conducted in two phases. In the first phase, we evaluated the reproductive factors, anthropometric parameters and past medical histories of participants of an ongoing multicentric clinical trial. In the second phase, we performed an extensive review of the literature for studies that had considered patients with a histologic-proven diagnosis of IGM without date limitations, and extracted the data about parity, breastfeeding, oral contraceptive pill use and past medical histories. We then carried out a meta-analysis.

Results: Data of 123 patients were included. The mean age was 35.11±7.07 years, and the mean body mass index was 27.41±4.74. Overall, %93.8, 90.27% and 28.7% of patients were parous, had breastfed, and had used OCP, respectively. Hypothyroidism represented the most common (18.94%) previous medical disease. We included 89 studies in our search. Considering these studies and ours, the pooled prevalence of rates of parity, breastfeeding and oral contraceptive pill consumption were 96%, 89%, and 29%; and the pooled prevalence of hypothyroidism, diabetes and hypertension were 9%, 5% and 5%, respectively. Although not exactly comparable, these rates of hypothyroidism were higher than those reported in women in the general population (4.2% in one large study in Iran).

Conclusion: Our study suggests a possible relation between a past history of hypothyroidism and IGM. We propose a study that investigates the occurrence of IGM in some large cohorts of healthy women, and the retrospective assessment of thyroid tests in the primary serum samples.

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INTRODUCTION

Idiopathic granulomatous mastitis (IGM) is a rare chronic disease of the breast.[1,2] The actual incidence of the disease is not known and is very diverse in various geographic areas; however, a

prevalence of 2.4 in 100,000 women between 20 to 40 years of age was reported for IGM in a study in the USA[3], and a recent review showed that the number of patients reported in studies was highest in Turkey, Iran, and China;[4] the incidence in India also is not very low.[5]

IGM mostly occurs in reproductive ages in women who have given birth to children and breastfed them.[6] The clinical image may include breast lumps or thickenings, skin and nipple changes involving edema, retraction, dimpling and ulcers, superficial or parenchymal inflammation and even infection presenting as mastitis or abscess.[6] The diagnosis of IGM is based on histologic examination which rules out other granulomatous diseases and malignancy.[1,6,7]

The etiology is unknown, but several possible causes have been put forward. Hormonal effects are mostly mentioned as risk factors, due to its association with sex-hormone related events such as gestation or consumption of oral contraceptive pills (OCPs). Microbial pathogenesis has likewise been blamed secondary to a high rate of detection of Corynebacterium species in assessments of IGM specimens, although these also constitute the normal flora of the breast ducts. Also, an autoimmune origin has been presumed for IGM.[2,8] The latter is the most likely due to the rather beneficial effects of corticosteroids and immunosuppressors in the management of IGM, the detection of immunologic laboratory markers in patients, the occurrence of immunologic events like erythema nodosum or peripheral arthritis in some patients, and the similarity of IGM and some autoimmune diseases such as granulomatous thyroiditis and granulomatous prostatitis.[9,10] Interestingly, a history of a previous thyroid disorder has been reported in several case reports of IGM.[11-13]

Most studies about IGM are retrospective, and the scarcity of prospective research on this subject implies the shortage of well- documented records about this disease. Multiple studies have also been carried out in our country about IGM. However, the prospective studies include low number of patients, maximally around or less than 30.[14,15] Four studies in Iran include more than 100 patients, and they are all retrospective. One of these studies (206 patients) did not include reproductive factors and reported no underlying or past medical diseases among the patients.[16] In one study (112 patients), all patients had breastfed and around half had consumed OCPs, but other reproductive factors and medical diseases have not been reviewed.[17] Another study (374 patients) found that around 95% and 87% of participants were parous and had breastfed, respectively.[1] In the fourth study (474 patients), these figures were respectively around %91 and 83%.[6] The latter 2 studies did not consider underlying diseases, except for a rate of 6% for diabetes in the last one.[17] To compensate for this lack of prospective data, we carried out the first part of the present study to investigate the association of IGM and other medical disorders as well as reproductive factors in a prospective setting. The aim of the second part of the study, consisting of a systematic review and meta-analysis, was to detect the rate of occurrence of the main variables and findings of the first phase in the existing literature, and perform a consistent analysis to find out their pooled prevalence considering the previous studies and ours.

METHODS

The present study consists of two phases: the first phase is an interim investigation of the primary data obtained through a larger study. The original prospective study is registered as a multicenter clinical trial in the Iranian Registry of Clinical Trials (IRCT, registration reference: IRCT20100706004329N10), has been approved in the Research Deputy of Tehran University of Medical Sciences (Approval Code: 99-3-259-50663), and has been approved ethically by the Ethics Committee of Tehran University of Medical Sciences (Approval Code: IR.TUMS.SINAHOSPITAL.REC.1400.012). This large trial compares three types of treatment of IGM and the inclusion criteria are the pathologic diagnosis of granulomatous mastitis in a woman presenting with relevant clinical signs and symptoms in the non-treated acute phase of the disease. The exclusion criteria consist of fungal infection of the breast, tuberculosis, fever that is not related to the mastitis or the abscess formed in the IGM lesion, polyarthritis or polyarthralgia, generalized lymphadenopathy, pregnancy and lactating status. At entry, a form is filled out by the patient for general and demographic data. Then, anthropometric variables are measured and medical data are asked by a trained interviewer. The medical data embrace many variables including the patients' past medical history and reproductive data. For the former, a history of diabetes, thyroid dysfunction, gynecologic disease, tuberculosis, or sarcoidosis proved by available laboratory evaluation or under treatment by a physician, as well as the past history of erythema nodosum and a category named "other" including any other diseases, is asked and recorded. Present general or breast Tuberculosis is ruled out for all patients by a standard PPD test and PCR of the specimens. More data regarding the methods of the main study are available on the site of IRCT at https://en.irct.ir/trial/55924. In the present study, we have evaluated the reproductive factors, anthropometric parameters and past medical histories of participants in the original prospective clinical trial.

The second phase of this study consists of an extensive search of the literature in PubMed, Scopus and Google Scholar using the keyword

"granulomatous mastitis". All case series, observational or cohort studies and clinical trials, whether retrospective or prospective, in English, French and Farsi were considered without any date limitation. Inclusion criteria entailed studies that had only included cases with a histologic-proven diagnosis of IGM, and contained information about at least two of the main variables we looked for, consisting of patients' ages, their pregnancy and lactation histories, their histories of OCP consumption, and their underlying diseases. Exclusion criteria were case reports and review articles, and studies lacking the inclusion criteria. We extracted all the data about parity, breastfeeding, OCP use and past medical histories reported in the retrieved papers. Thereafter, we carried out a meta-analysis of these data, including our study.

Statistical analysis

The data of the first phase were analyzed by IBM SPSS 24 (IBM Corp. Released in 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp). Continuous variables are presented as mean ± standard deviation, and categorical variables are shown as numbers with percentages.

In the next phase for the evaluation of existing studies, including ours, we used the I^2 index and Q test at 5 percent significant level (P<0.05) to investigate between study heterogeneity. We used random effects model to pool the prevalence of the past medical histories of patients because of the high between study heterogeneity (I^2=75.32, P-value=0.001). We had some proportions near boundaries (near zero or 100); therefore, to estimate the exact and score test-based confidence interval for this proportions, we used the metaprop command. Finally, we used forest plot to show the pooled prevalence.

We did not assess the publication bias, because the prevalence is always a positive number, so the symmetry in the funnel plot is not due to the publication bias. All the analysis was performed by STATA11 (StataCorp, College Station, TX, USA).

RESULTS

Overall, the data of 123 patients had been recorded in our original prospective study up to the time of this report. The mean age of our patients was 35.11 ± 7.07 years old, and the mean body mass index (BMI) was 27.41± 4.74.

Table 1 shows the reproductive data of all the participants. The median gravidity and parity were two, and the largest proportion of the patients were fertile, had not aborted, and had not used OCPs. Among the 123 participants, 95 patients provided their previous histories of diseases as they were asked in our forms; this information is also shown in Table 1.

As demonstrated, hypothyroidism (HoT) represented the most common underlying disorder.

As shown in Figure 1, in our review of the existing literature, we retrieved 359 studies from PubMed, 420 studies from Google scholar (42 pages), and 872 studies from Scopus. After the first and second screening, we had 89 articles which fulfilled our eligibility criteria. The data of all the entered studies are available in Table 1 of the supplementary material.

The rate of parity among the participants, meaning the percentage of patients who had given birth to one or more children, had been reported in 68 studies. The rate of breastfeeding, meaning the percentage of patients who had breastfed, was reported in 43 studies. Four studies had only mentioned the mean duration of breastfeeding in their patients, and three had only given the mean parity among participants. These latter studies are included in the supplementary table but could not be used in the meta-analysis.

Table 2 of the supplementary material categorizes the studies according to the rates of parity and breastfeeding. The objective of this table is to demonstrate the number of studies and more importantly, the sample size of the studies which had found different rates. The pooled prevalence of the rate of parity, breastfeeding and OCP consumption among all the participants in these studies is demonstrated in Table 2, and Figure 2 illustrates these findings as forest plots.

Among all the studies, 48 pointed to the underlying or previous medical histories of the participants. Most of them only mentioned the history of diabetes or hypertension, or only pointed out that the patients had no background disease. A few have reported the frequency of various diseases in their patients. It could not be understood from the papers whether patients had been asked about specific disorders- specifically hypothyroidism for our purpose- or if they had only asked a general question about previous diseases. Table 3 of the supplementary material shows the stated diseases and the range of the mean frequency reported in the articles. The pooled prevalence of past medical diseases that had been reported in more than one study among all the participants in these studies is shown in Table 2. Figure 2 illustrates the findings related to hypothyroidism in these studies as a forest plot.

Table 1. Reproductive data and past systemic diseases in all the participants

Variable		Number	Percent	Mean	SD	Range
Gravidity	0	6	4.9	2.12	1.26	0-7
	1	32	26.0			
	2	34	27.6			
	3	33	26.8			
	4 or more	7	5.6			
	Missing	10	8.1			
Parity	0	6	4.9	1.80	1.01	0-7
	1	37	30.1			
	2	50	40.7			
	3	17	13.8			
	4 or more	2	1.6			
	Missing	10	8.1			
Abortion	0	86	69.9	0.31	110	0-4
	1	22	17.9			
	2 or more	5	4			
	Missing	10	8.1			
Age at 1st pregnancy (10 Missing)		-	-	23.69	4.50	15-35
Breastfeeding time	In those who had children (months) (N=102)			34.83	36.26	0-336
	In all participants (months) (N=108)			32.89	36.13	0-336
	Missing	15		-	-	-
Age of menarche (21 Missing)		-	-	12.75	1.70	9-18
History of infertility	No	106	86.2	-	-	-
	Yes	4	3.3			
	Missing	13	10.6			
OCP consumption*	No	77	62.6	-	-	-
	Yes	31	25.2			
	Missing	15	12.2			
Past systemic diseases	Hypothyroidism	18	18.94	-	-	-
	Diabetes	7	7.36			
	Rheumatic disease	3	3.15			
	Depression	3	3.15			
	Tuberculosis	2	1.55			
	Anemia	1	1.05			
	Hyperthyroidism	1	1.05			
	Hypertension	1	1.05			
	Multiple sclerosis	1	1.05			
	Sarcoidosis	0	0			
	Erythema nodosum	0	0			

*Defined as more than 5 years of consumption. OCP= oral contraceptive pills, SD= standard deviation

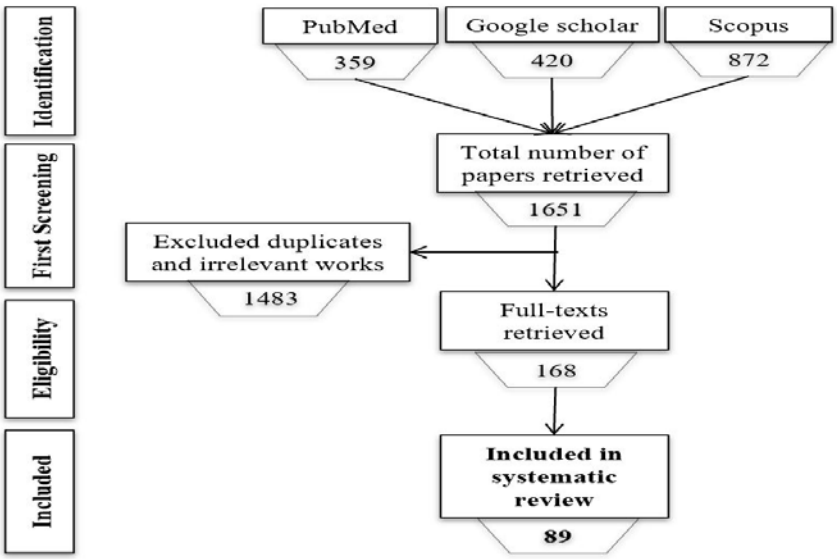

Figure 1. Flowchart of search protocol and study inclusion

Table 2. Pooled prevalence of past medical diseases and rates of parity, breastfeeding and oral contraceptive pill consumption

Variable	Number of studies	Total sample size	Pooled prevalence % (95% CI)	I^2 %	P-value
Past systemic disease					
Diabetes	19	2236	5 (3 to 6)	55.05	0.001
Hypertension	10	1339	5 (3 to 8)	68.13	0.001
Autoimmune disease	3	773	2 (1 to 3)	-	-
Erythema nodosum	3	54	9 (2 to 19)	-	-
Sarcoidosis	3	144	2 (0 to 7)	-	-
Tuberculosis	6	339	3 (1 to 7)	44.42	0.11
Hypothyroidism	5	407	9 (3 to 16)	79.07	0.001
Reproductive factors					
Parity	64	3976	96 (94-97)	75.31	0.001
Breastfeeding	40	3089	89 (84 to 93)	92.5	0.001
OCP	47	3297	29 (21 to 38)	96.08	0.01

OCP= oral contraceptive pills

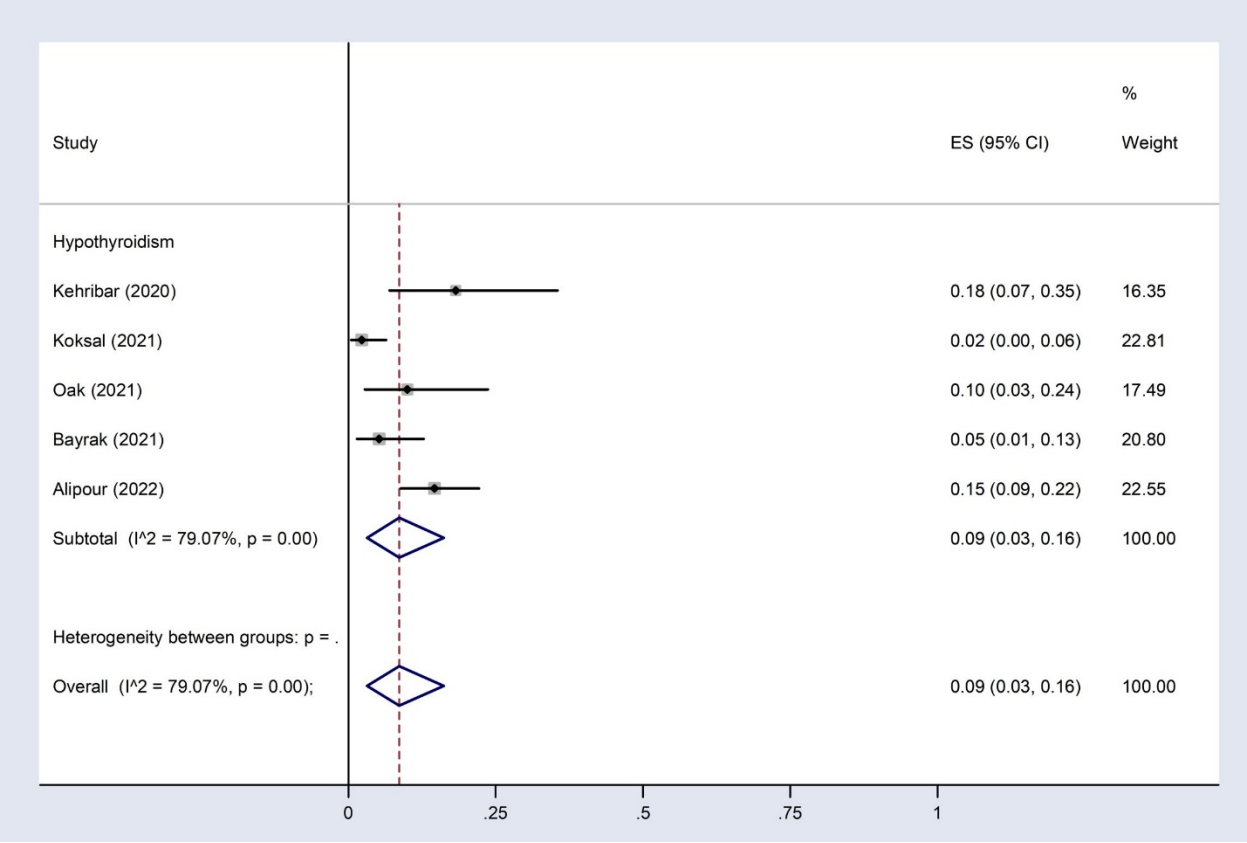

Figure 2. Forest plot of the pooled prevalence of hypothyroidism in six studies

DISCUSSION

In this study, we assessed the reproductive factors in 123 patients with IGM and investigated their past medical histories. Interestingly, we found a high rate of previous HoT in our patients.

The mean age of participants was around 35 (22-73) years in our study, which was around the same as in most existing studies; however, the age range was largely fluctuating: the youngest patient was 11 and the oldest was 83 in previous studies.

A possible etiopathologic relation with sex hormones has been mentioned for IGM due to the high rate of parity and breastfeeding or OCP use in IGM patients [2, 8]; this has even been stated as the cause of the higher incidence of IGM in the Middle East.[18] In our study, after excluding the missing cases, %93.8, 90.27% and 28.7% of patients were parous, had breastfed, and had used OCP, respectively. In previous studies that gave data about this variable, the mean rate of OCP usage was 29%. This rate of OCP consumption is not high and does not induce the suggestion that contraceptives could be an etiologic factor for IGM. However, the mean rates of parity and childbearing were as high as ours (96% and 89%, respectively) in most studies; only seven studies found a less than 80% rate of positive parity, and most of these involved a low sample size. These high rates of parity call up an etiological association. However, the common age of the disease is in reproductive ages, and the geographical distribution is in areas with high

Supplementary Table 2. Categorization of studies and their sample size according to their reported rates of parity and breastfeeding

	First Author, Year (number of patients)*
100% parous in 24 studies	CDC, 2009 (N=7); Sakura, 2011 (N=8); Ocal, 2010 (N=16); Gurleyik, 2012 (N=19); Al-Jarrah, 2013 (N=20); Baslaim, 2007 (N=20); Dag, 2021 (N=20); Liu, 2018 (N=22); Kiyak, 2014 (N=24); Sheybani, 2015 (N=28); Elzahaby, 2016 (N=30); Montazer, 2020 (N=30); Yildiz, 2015 (N=30); Yildirim, 2021 (N=36); Pourzand, 2014 (N=38); Vanovcanova, 2019 (N=39); Mahmodlou, 2017 (N=48); Girgin, 2015 (N=49); Tang, 2020 (N=49); Helal, 2016 (N=65); Helal, 2016 (N=65); Prasad, 2017 (N=73); Li, 2018 (N=75); Yücesoy, 2021 (N=93)
90-99% parous in 26 studies	Al-Khaffaf, 2008 (N=18); Bani-Hani, 2004 (N=24); Joseph, 2014 (N=24); Lee, 2006 (N=31); Steuer, 2020 (N=32); Erozgen, 2010 (N=33); Emre, 2018 (N=34); Alikhassi, 2019 (N=36); Tekin, 2020 (N=37); Oak, 2021 (N=40); Williams, 2021 (N=42); Omranipour, 2013 (N=43); Chirappapha, 2018 (N=44);
	Oran, 2013 (N=46); Mizrakli, 2015 (N=49); Lin, 2021 (N=50); Tekgoz, 2020 (N=53); Kundaktepe, 2021 (N=64); Yaghan, 2019 (N=68); Bayrak, 2021 (N=77); Toktas, 2020 (N=78); Davis, 2019 (N=120); Koksal, 2021(N=134); Kaviani, 2019 (N=374); Azizi, 2020 (N=474); Uysal, 2017 (N=720)
80-89% parous in 9 studies	Akahane, 2013 (N=12); Yau, 2010 (N=12); Konan, 2012 (N=15); Fazzio, 2016 (N=17); Freeman, 2017 (N=17); Postolova, 2019 (N=19); Salehi, 2017 (N=26); Pandey, 2014 (N=49); Tan, 2019 (N=113)
60-79% parous in 5 studies	Yukawa, 2015 (N=13); Skandarajah, 2014 (N=17); Neel, 2013 (N=23); Barreto, 2018 (N=37); Chirappapha, 2018 (N=44)
<60% parous in 2 studies	Lai, 2005 (N=9); Calis, 2014 (N=13)
100% positive history of breastfeeding in 13 studies	CDC, 2009 (N=7); Al-Jarrah, 2013 (N=20); Baslaim, 2007 (N=20); Sheybani, 2015 (N=28); Elzahaby, 2016 (N=30); Montazer, 2020 (N=30); Yildiz, 2015 (N=30) Yildirim, 2021 (N=36); Mahmodlou, 2017 (N=48); Girgin, 2015 (N=49); Helal, 2016 (N=65); Yücesoy, 2021 (N=93); Kadivar, 2016 (N=112)
90-99% positive history of breastfeeding in 10 studies	Ocal, 2010 (N=16); Joseph, 2014 (N=24); Erozgen, 2010 (N=33); Alikhassi, 2019 (N=36); Omranipour, 2013 (N=43); Mizrakli, 2015 (N=49); Tekgoz, 2020 (N=53); Li, 2018 (N=75); Koksal, 2021(N=134); Wang, 2019 (N=200)
80-89% positive history of breastfeeding in 7 studies	Gunduz, 2014 (N=11); Dag, 2021 (N=20); Salehi, 2017 (N=26); Steuer, 2020 (N=32); Kaviani, 2019 (N=374); Azizi, 2020 (N=474); Uysal, 2017 (N=720)
60-79% positive history of breastfeeding in 4 studies	Gurleyik, 2012 (N=19); Pandey, 2014 (N=49); Kundaktepe, 2021 (N=64); Shojaee, 2021 (N=87)
<60% positive history of breastfeeding in 7 studies	Calis, 2014 (N=13); Yukawa, 2015 (N=13); Boufettal, 2012 (N=20); Neel, 2013 (N=23); Lee, 2006 (N=31); Vanovcanova, 2019 (N=39); Jeon, 2017 (N=43)

*In each row, studies are mentioned in ascending order of their sample sizes

rates of childbearing. Whether the high rate of parity as a cause of IGM causes the high incidence in those areas and ages, or whether other factors like genetics, common microbial agents and environmental conditions have caused the high incidence in that geography and age, which potentially leads to a high parity rate, cannot be decided for now, although the former seems more plausible. Nevertheless, parity and breastfeeding, or overall reproductive and hormonal features can be considered as strong risk factors for IGM. Moreover, IGM has also been reported in men, although rarely. There is a possibility that the affected men had unrecognized sex hormonal abnormalities, otherwise this fact might be either

Supplementary Table 3. Past or underlying diseases stated in included studies and the range of the reported mean frequencies

Past medical history or underlying disease	First author, year (number of patients)
None, in 15 studies	Sakura, 2011 (N=8); Lai, 2005 (N=9); Akahane, 2013 (N=12); Yau, 2010 (N=12); Yukawa, 2015 (N=13); Fazzio, 2016 (N=17); Freeman, 2017 (N=17); Bani-Hani, 2004 (N=24); Elzahaby, 2016 (N=30); Yildiz, 2015 (N=30); Alikhassi, 2019 (N=36); Pourzand, 2014 (N=38); Girgin, 2015 (N=49); Seo, 2012 (N=58); Aghajanzadeh, 2015 (N=206)
Diabetes: 1.3- 15%*, in 18 studies	Khalaf, 2020 (N=10); Ocal, 2010 (N=16); Skandarajah, 2014 (N=17); Baslaim, 2007 (N=20); Dag, 2021 (N=20); Barreto, 2018 (N=37); Jeon, 2017 (N=43); Chirappapha, 2018 (N=44); Kundaktepe, 2021 (N=64); Zhang, 2020 (N=68); Bayrak, 2021 (N=77); Yabanoglu, 2015 (N=77); Toktas, 2020 (N=78); Co, 2018 (N=102), Kadivar, 2016 (N=112); Koksal, 2021 (N=134); Azizi, 2020 (N=474); Uysal, 2017 (N=720)
Hypertension: 2- 17.6%, in 9 studies	Gunduz, 2014 (N=11); Baslaim, 2007 (N=20); Chirappapha, 2018 (N=44); Kundaktepe, 2021 (N=64); Zhang, 2020 (N=68); Yabanoglu, 2015 (N=77); Toktas, 2020 (N=78); Koksal, 2021 (N=134); Uysal, 2017 (N=720)
Autoimmune or Rheumatologic Diseases**: 0.8-13.3%, in 12 studies	Calis, 2014 (N=13); Konan, 2012 (N=15); Skandarajah, 2014 (N=17); Liu, 2018 (N=22); Neel, 2013 (N=23); Kehribar, 2020 (N=33); Barreto, 2018 (N=37); Oak, 2021 (N=40); Yabanoglu, 2015 (N=77); Ozsen, 2018 (N=90); Koksal, 2021 (N=134); Uysal, 2017 (N=720)
History of tuberculosis***: 1.1-11.1%, in 6 studies	Bashir, 2017 (N=18); Liu, 2018 (N=22); Pak, 2021 (N=30); Emre, 2018 (N=34); Chirappapha, 2018 (N=44); Ozsen, 2018 (N=90)
Thyroid disorders:	
Thyroiditis: 4.3%, in 1 study	Neel, 2013 (N=23)
Hyperthyroidism:2.7%, in 1 study	Barreto, 2018 (N=37)
Hypothyroidism: 2- 18.2%, in 4 studies	Kehribar, 2020 (N=33); Oak, 2021 (N=40); Bayrak, 2021 (N=77); Koksal, 2021 (N=134)
Others: 0.8- 7.8%, in 8 studies	Konan, 2012 (N=15); Skandarajah, 2014 (N=17); Pak, 2021 (N=30); Kundaktepe, 2021 (N=64); Yabanoglu, 2015 (N=77); Toktas, 2020 (N=78); Koksal, 2021 (N=134); Uysal, 2017 (N=720)

* Higher rates of diabetes are reported in studies with smaller sample sizes, high fasting blood sugar in 37.0% among 200 cases in Wang *et al.* (2019) study; Gestational diabetes in 38% of 42 patients of Altintoprak *et al.* study, 2015 and 9% of a study by Gunduz *et al.* (2014); ** various disorders including erythema nodosum, sarcoidosis and many others. Higher rates are reported in studies with smaller sample sizes; ***Pulmonary or abdominal

taken against the relation of female reproductive factors and the disease, or show that sex hormones play at most a partial role in the pathogenesis of IGM.

An unexpected finding in our study was a nearly 19% rate of previous HoT among our patients. The association of HoT and IGM had not been discussed in articles in the literature, but a relationship between granulomatous thyroiditis and IGM had been proposed in the past.[2,10] Therefore, we looked for the publications that had reported the rates of HoT in their IGM patients. Among all the studies, 41 had not assessed the underlying or previous systemic disease of their patients. In 44 studies, it is not clear whether the patients had been specifically asked about the history of HoT. Thus, it cannot be ascertained whether this information has been omitted in the patients' history, or whether the history was negative. Three retrospective studies involving 33,[9] 77,[19] and 134,[20] IGM patients in Turkey and one prospective study including 40 patients in India[5] had found a history of HoT in around 18%, 10%, 5% and 2% of their cases, respectively. The pooled rate of HoT in 5 studies (ours, and the four papers) was 9%, which is not a high rate.

We have not compared the rate of HoT in our patients with a control group, and neither have previous studies. However, data about the prevalence of HoT in the overall population can be found in the literature. The prevalence of HoT was 4.8% in women in Norway[21], the incidence of HoT was 13.5 (with a 6-fold preponderance in women) and 32.8 in 100,000 individuals per year in two studies in Denmark[22,23], and 4.1 in 1000 per year in women in the United Kingdom.[24] Primary (spontaneous, probably autoimmune) HoT constituted around 85% of the cases in Danish people[22], with an incidence of around 5 in 1000 people per year in the female general population of Scotland[25], and 3.5 in 1000 per year in women in the United Kingdom.[24] A study in Tehran, the capital city of Iran, has shown a yearly incidence of 0.28 per 1000 for HoT and 11.59 per 1000 for subclinical HoT in women.[26] Another study in Isfahan, one of the large cities in Iran, has found a prevalence of 4.2% and 8.6% for HoT and subclinical HoT in women, respectively.[27] The incidence of HoT is higher in older women.[28] As our data comprised overt hypothyroidism, and data of other papers apparently did not include subclinical HoT either

(because they had not performed thyroid function tests), the facts and numbers are in favor of a higher rate of HoT in these IGM patients compared with the general population. Whether these findings are just accidental, or IGM is one of the late complications of hypothyroidism or the result of its treatment cannot be justified for now. Moreover, previous subclinical hypothyroidism also has not been assessed in any study, including ours. This can only be performed by investigating cohorts of healthy women, and subsequent analysis of thyroid function in those who got IGM during follow up, which is hardly practical considering the low rate of IGM. We are measuring thyroid hormone levels in our original prospective study, but this will only clarify the present status of thyroid function in our patients.

Diabetes and hypertension were the next common past medical diseases in the pooled analysis; the rates were 5% for both. For comparison with the expected prevalence in the general population, we looked up figures that have been released in large scale studies and systematic reviews. The prevalence of diabetes in the general population was around 7.9% in women[29], in Iran the prevalence was 15.6% in women.[30] The prevalence of hypertension in women 30–79 years of age was around 32% worldwide[31], and 24% in Iran.[32,33] Therefore, contrary to hypothyroidism, these two diseases were not more prevalent in IGM patients. The low prevalence might be due to the young age of the participants.

We searched for a pathophysiological explanation behind our proposed relationship between HoT and IGM. We reached one probable hypotheses: it has been seen that inflammatory markers rise in HoT[34,35], and return to normal with treatment. This may be the basis for the inflammation occurring in the breast in patients with previous HyT. Obviously, a more robust logic might exist, which should be further investigated if the association between previous HoT and IGM proves true in future studies.

Our study had some limitations. We did not have a control group, so we could not compare the rates of hypothyroidism, hypertension, and diabetes between IGM patients and healthy people. Also, we did not have the results of thyroid function tests and the present status of thyroid function, so we only mentioned the established history of thyroid disorders. We have planned to check thyroid function tests in the ongoing original prospective study.

In summary, our study suggests that an association between a history of HoT and IGM might exist, but this needs to be investigated properly by future studies. We propose a study that investigates the occurrence of IGM in some large cohorts of healthy women, and the retrospective assessment of thyroid tests in the primary serum samples. Meanwhile, our ongoing clinical trial might clarify some further points in this regard, and we are planning for a large prospective basic study about the underlying diseases and causes of IGM.

ABBREVIATIONS

IGM: Idiopathic Granulomatous Mastitis; OCP: Oral Contraceptive Pills; BMI: Body Mass Index; Hot: Hypothyroidism.

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ETHICAL CONSIDERATIONS

The Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran approved the study (Approval Code: IR.TUMS.SINAHOSPITAL.REC.1400.012). All participants read and signed a written informed consent before entering the study.

DATA AVAILABILITY

All data analyzed during this study are included in this published article and row-data are available from the corresponding author on reasonable request.

CONFLICT OF INTERESTS

The authors have no conflict of interest to declare.

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