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META ANALYSIS

Gynecomastia in Children; A Meta-analysis Study

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Abstract

Background: **Gynecomastia is a broadening of the glandular breast tissue and overlying skin in boys. The infection handle is related with uneasiness, trouble, decreased quality of life, and an unsuitable body picture.**

The aim of the study: **To a meta-analysis Study of gynecomastia in children, through a process of combining the results of individual studies with statistical methods in one review, regarding the etiology, and management.**

Patients and methods: **this study was conducted in accordance with the Preferred Reporting Items for Meta-Analyses (PRISMA) statement (Moher et al., 2009).**

Results: **The starting look of distinctive databases, said some time recently, had recognized 521 reports from which 84 reports have been prohibited by EndNote program as copies. The titles and abstracts of the remaining 437 reports were screened, and revealed exclusion of 355 reports for not meeting the inclusion criteria. The complete writings of the remaining 82 reports, from the title and unique screening, were screened for qualification criteria. After prohibition of 58 reports, 24 papers of different study designs were eventually included for systematic review.**

Conclusion: **This systematic review and meta-analysis investigated the different etiological, clinical and therapeutic aspects of pediatric and peripupertal gynecomastia. Pediatric gynecomastia was significantly more associated with higher BMI and E2/T ratio. Imbalance between estradiol to testosterone levels and the increased sensitivity of estradiol are the main pathological mechanisms. Several techniques have been proposed in the literature to address gynecomastia. The combined use of surgical excision and aspiration techniques seems to reduce the rate of complications compared to surgical excision alone.**

Keywords: Gynecomastia, Estradiol, Testosterone, Aspiration, Excision

1. Introduction

Gynecomastia is a broadening of the glandular breast tissue and overlying skin in boys. The infection handle is related with uneasiness, trouble, decreased quality of life, and an unsuitable body picture.[1] A few gauges are that glandular expansion happens in generally 65% of juvenile guys, but most of these cases resolve without any therapeutic or surgical mediation with only 7.7% of patients having persistent gynecomastia beyond their teenage years.[2] The etiology of gynecomastia remains unclear. Gynecomastia may be unilateral, bilateral, or asymmetric, most cases of gynecomastia are thought to result from an awkwardness between estrogens and androgens. Gynecomastia is uncommon in prepubertal matured boys. It is related to outright or relative estrogen abundance is show: with exogenous admissions, endogenous generation, or with expanded fringe transformation of androgens to estrogens auxiliary to plenteous aromatase movement, androgen insufficiency, or androgen cold-heartedness.[3] Administration of gynecomastia is based on the seriousness and classification of the malady and the psychosocial trouble it creates within the quiet which, started by observation and reassurance are widely regarded as the safest and most reasonable treatment. Gynecomastia is self-limited in 75−90% of pediatrics and regresses over 1−3 years.[4] Therapeutic treatment of gynecomastia points to redress the estrogen-androgen lopsidedness[5] Surgery may be considered in case no relapse

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is watched after a period of perception of at slightest one year. Surgical procedure may be utilized in gynecomastia is Subcutaneous nipple-sparing mastectomy and liposuction, or both.[6] This study aimed to systematically review and meta-analyze the pooled data related to etiology, and management of pediatric gynecomastia.

2. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement was followed when conducting this meta-analysis.[7] Agreeing to our institution's approach, conducting the think about did not require ethical approval.

2.1. Eligibility criteria

We included any report describing the clinical presentations and internationally accepted diagnostic classifications and scoring systems of gynecomastia in children and adolescents less than 18 years old. We also included studies, concerning with the investigations and management of pediatric and adolescent gynecomastia. No limitation was taken with respect to certain populace, put, ethnicity, dialect, or distribution date. We avoided letters, publication comments, proposition, surveys, book chapters, news, or only-abstract articles. We too prohibited papers in the event that their information was unimportant or cannot be extricated. Blended populace of distinctive age bunches were avoidance populace over 18 a long time.

2.2. Search strategy and study selection

A comprehensive writing seek for important articles was performed up to admirable, 2022 utilizing PubMed, Scopus, Web of Science (ISI), Google Researcher, Popline, Worldwide Wellbeing Library (GHL), Virtual Wellbeing Library (VHL) counting Cochrane database, NYAM (Unused York Institute of Pharmaceutical), and SIGLE (Framework for Data on Dim Writing in Europe). The used search string was ('Pediatric gynecomastia, Adolescent Gynecomastia, Pubertal Gynecomastia, Prepubertal Gynecomastia', 'Conservative management, Medical management, classification, Surgical techniques, Reduction mammoplasty, Subcutaneous mastectomy, Liposuction, Aspiration OR Endoscopic'). This string was altered to coordinate each database. Look comes about were recovered and copies were evacuated utilizing EndNote X7.4 program for Windows. Two independent reviewers candidate and supervisors screened the proposed articles in arrange to incorporate the pertinent ones concurring to our consideration and avoidance criteria. Screening title and unique happened at first, taken after by full-text screening. Difference was settled by dialog and agreement between reviewers and a senior observer.

2.3. Data extraction

Candidate extricated the information of intrigued from the included articles utilizing the standardized extraction frame. Any inconsistency was settled by dialog to reach the agreement. The extraction shape was created by a pilot extraction of all chosen papers. The extricated factors included socioeconomics of the included patients. We extracted data related to the clinical characteristics, risk factors, clinical and surgical management of pediatric gynecomastia. If data was presented as graph only, it was extracted using Plot Digitizer software (http://plotdigitizer.sourceforge.net/).

2.4. Risk of bias assessment

The risk of bias assessment tool is determined according to the study design of the included papers. National Heart, Lung, and Blood Institute (NHLBI) tool for quality assessment is used for cohort and cross-sectional studies in addition to case control studies. Fourteen well-organized questions were proposed to survey the think about populace, test estimate, presentation, result, follow-up and the bewildering factors. Candidate assesses the risk of bias &any discrepancy was resolved by supervisor.

2.5. Statistical analysis

The meta-analysis was carried out using Comprehensive Meta-Analysis software (version 2). The arbitrary impact demonstrate was utilized when there was critical heterogeneity, while the settled impact show was utilized when there was no noteworthy heterogeneity. The $\chi 2$ test and I2 statistics were used to assess statistical heterogeneity. Significant heterogeneity was considered when the *P*-value for the $\chi 2$ test was <0.1 or the I^2 test value was >50%. To present continuous data, mean difference (MD) and 95% confidence interval (95% CI) were used; otherwise, standardized mean difference (SMD) was appropriate

3. Results

3.1. Search results and characteristics of included studies

The starting look of distinctive databases, said some time recently, had recognized 521 reports from which

84 reports have been prohibited by EndNote program as copies. The titles and abstracts of the remaining 437 reports were screened, and revealed exclusion of 355 reports for not meeting the inclusion criteria. The complete writings of the remaining 82 reports, from the title and unique screening, were screened for qualification criteria. After prohibition of 58 reports, 24 papers of different study designs were eventually included for systematic review. The manual look of references of the included papers did not incorporate any assist papers (Fig. 1). Table 1 represented obesity and hormonal characteristics in the included studies.

The 24 papers were further subclassified into three categories, Eleven studies discussed the association between BMI, obesity, hormonal dysregulation and the development of pubertal gynecomastia. All the studies compared gynecomastia to control group, regarding BMI, testosterone, estradiol, FSH, LH and E2/T ratio (Ozkan et al., 2021,[17] Ibrahim et al., 2013,[8] Kilic et al., 2011,[11] Reinehr et al., 2020,[10] ERSOZ et al., 2002,[13] Nuzzi et al., 2013,[14] Mieritz et al., 2014,[9] and Dündar et al., 2005[12]).

Four studies described the medical intervention of pubertal and pediatric gynecomastia (Derman et al., 2003,[18] Derman et al., 2008,[19] König et al., 1987,[20] Lawrence et al., 2004[21]).

Nine studies discussed the different surgical techniques (Zavlin et al., 2017[1]; Choi et al., 2017[22]; Gabra et al., 2004[23]; Celebioglu et al., 2004[24]; Fischer et al., 2014[25]; Laituri et al., 2009[26]; Varlet et al., 2019[27]; Peters et al., 1998[28]; Rosen et al., 2010[29]).

3.2. Meta-analysis

The meta-analysis was done on 8 papers (Ozkan et al., 2021,[17] Ibrahim et al., 2013,[8] Kilic et al., 2011,[11] Reinehr et al., 2020,[10] ERSOZ et al., 2002,[13] Nuzzi et al., 2013,[14] Mieritz et al., 2014,[9] and Dündar et al., 2005[12]) (Fig. 1). The total number of gynecomastia patients in the included studies for meta-analysis was 1724 patients. The 8 papers compared gynecomastia (n = 621 patients) to control, having no gynecomastia (n = 1093 patients). Variables eligible for meta-analysis were BMI, testosterone, estradiol, FSH, LH, E2/T ratio.

4. Outcomes

4.1. Obesity and hormonal dysregulation associated with gynecomastia

We included 8 papers in this meta-analysis, with a total number of 1724 gynecomastia patients. All the studies compared gynecomastia (n = 631) to control healthy group (n = 1093).

(1) Regarding BMI, 8 papers compared gynecomastia to control with a total number of 1724 patients (Ozkan et al., 2021,[17] Ibrahim et al., 2013,[8] Kilic et al., 2011,[11] Reinehr et al., 2020,[10] ERSOZ et al., 2002,[13] Nuzzi et al., 2013,[14] Mieritz et al., 2014,[9] and Dündar et al., 2005[12]). The meta-analysis revealed that BMI showed significant difference scores among the control group, evidenced by the reported mean difference (MD = 3.2, 95% CI 1.67–4.74, $P = 0.0001$) (Fig. 3).

(2) In addition, 4 papers compared gynecomastia to control, regarding testosterone (Ibrahim et al., 2013,[8] Kilic et al., 2011,[11] ERSOZ et al., 2002,[13] Mieritz et al., 2014[9]). The overall number of patients included were 864 patients (Gynecomastia = 308, Control = 556). No statistically significant difference was reported between gynecomastia and control regarding testosterone (P value = 0.06) (Fig. 4).

(3) Regarding estradiol, 6 papers compared gynecomastia to control with a total number of 1035 patients (Gynecomastia = 414, Control = 621). Estradiol level was higher in the gynecomastia group, but no statistically significant difference was reported between the 2 groups (P value = 0.1) (Fig. 5) (Ibrahim et al., 2013,[8] Kilic et al., 2011,[11] Reinehr et al., 2020,[10] ERSOZ et al., 2002,[13] Mieritz et al., 2014,[9] and Dündar et al., 2005[12]).

(4) Five papers compared gynecomastia to control with a total number of 925 patients (Gynecomastia = 352, Control = 573). Similarly, FSH did not appear any noteworthy contrast between the 2 bunches (P value = 0.14) (Fig. 6) (Ibrahim et al., 2013,[8] Reinehr et al., 2020,[10] ERSOZ et al., 2002,[13] Mieritz et al., 2014,[9] and Dündar et al., 2005[12]).

(5) A total of 492 patients were included for meta-analysis regarding LH (Gynecomastia = 209, Control = 283). No significant difference was reported between the 2 groups (P value = 0.2) (Fig. 7) (Ibrahim et al., 2013,[8] Reinehr et al., 2020,[10] ERSOZ et al., 2002,[13] Mieritz et al., 2014,[9] Kilic et al., 2011[11]).

(6) Regarding the ratio E2/T, 4 papers were included for the meta-analysis with a total number of 406 patients (Gynecomastia = 168, Control = 238). This study revealed that E2/T ratio was significantly higher in the gynecomastia group compared to the control group (MD = 3.38, 95% CI 1.58–5.17, $P = 0.0002$) (Fig. 8) (Reinehr et al., 2020,[10] ERSOZ et al., 2002,[13] Mieritz et al., 2014,[9] and Dündar et al., 2005[12]).

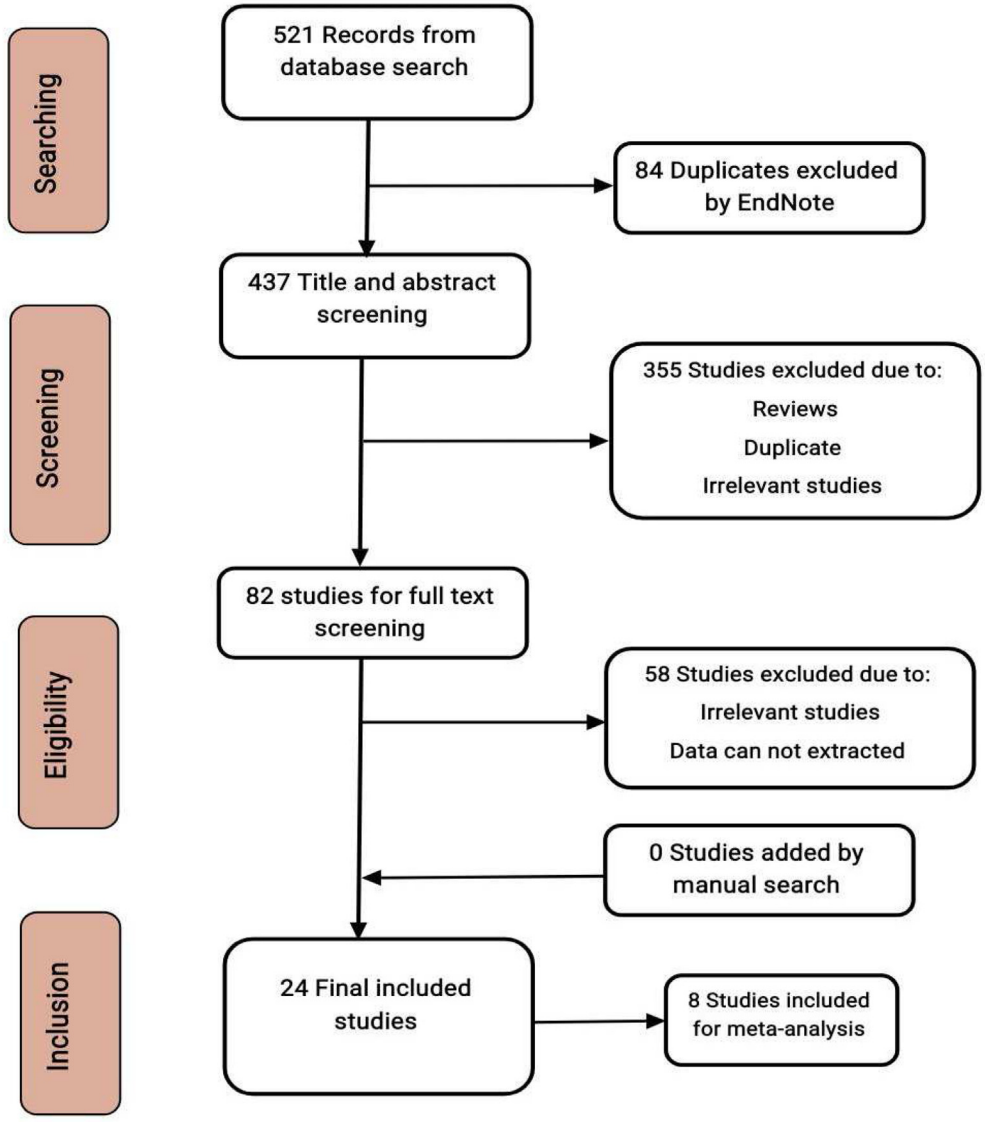

Fig. 1. Flow diagram of the included studies.
1. Was the research question or objective in this paper clearly stated?
2. Was the study population clearly specified and defined?
3. Was the participation rate of eligible persons at least 50%
4. Were all the subjects selected or recruited from the same or similar populations?
5. Was a sample size justification, power description, or variance and effect estimates provided?
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome being measured?
7. Was the timeframe sufficient to see the outcomes?
8. For exposures that can vary in amount or level, did the study examine different levels of the exposures as related to outcome?
9. Were the exposure measures (independent variables) clearly defined, valid, reliable and implemented consistedently across all study participants?
10. Was the exposure(s) assessed more than once over time?
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable and implemented consistedently across all study participants?
12. Were the outcome assessors blinded to the exposure status of participants?
13. Was loss to follow-up after baseline 20% or less?
14. Were key potential confounding variables measured and adjusted statistically?

4.2. Heterogeneity assessment

Heterogeneity was significantly reported in all the meta-analysis variables except for testosterone, evidenced by the I2 and *P* value. Variables BMI, Estradiol, FSH, LH, E2/T showed I2>50% (I2 88%, $P = 0.000$; I2 72%, *P* 0.003; I2 94%, *P* 0.000; I2 86%, *P* 0.000; I2 64%, *P* 0.04). Conversely, no significant heterogeneity was reported, regarding testosterone (I2 28%, *P* 0.25).

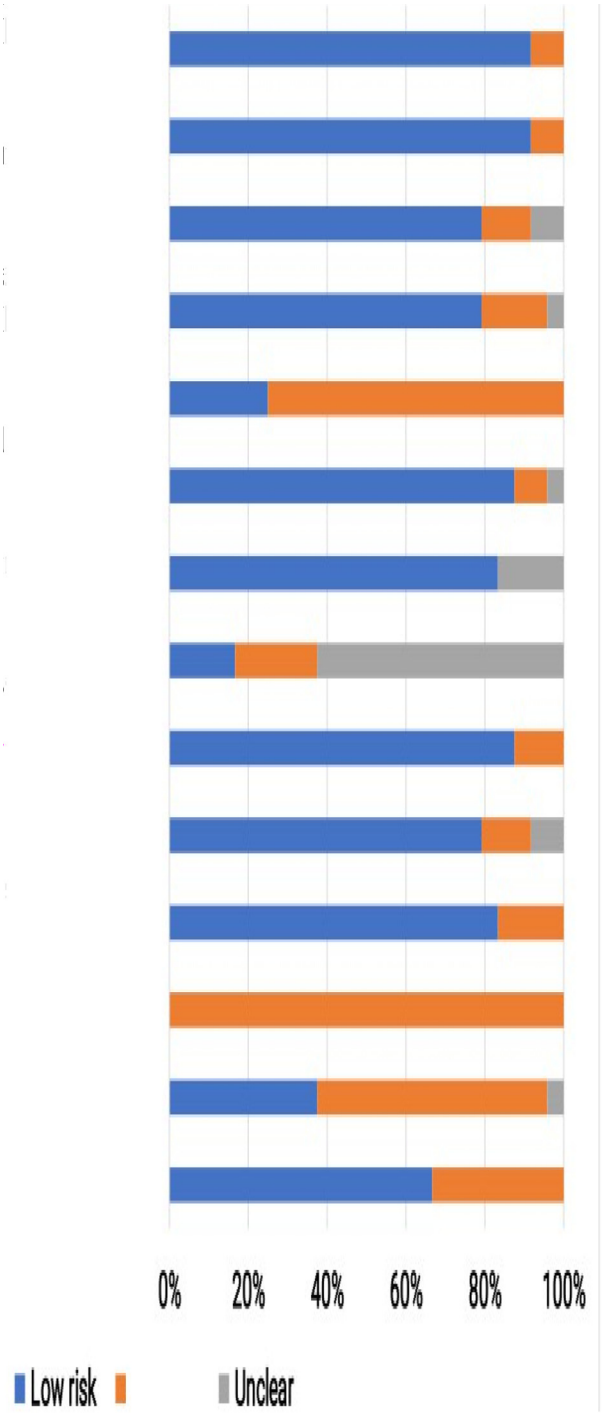

Fig. 2. NHLBI tool for risk of bias assessment.

4.3. Clinical characteristics and staging of gynecomastia

We reported that gynecomastia presented bilaterally in the majority of cases (37%), whilst it was unilateral in (21%) of cases. Regarding tanner staging, majority of the cases were stage 1 or 2 (66%), stage 1 (32%) and stage 2 (34%). Stage 3 and 4 represented the minority of cases (34%), stage 3 (21%) and stage 4 (13%) (Fig. 9) (Table 2).

4.4. The conservative management of pediatric gynecomastia

Four papers were included in this systematic review, discussing the medical management of pediatric and adolescent gynecomastia (Derman et al., 2003,[18] Derman et al., 2008,[19] König et al., 1987,[20] Lawrence et al., 2004[21]). König et al. prescribed 20–40 mg tamoxifen per day for 2–12 months. Out of 10 participants, eight had full determination and two had fractional determination. In addition, Lawrence et al. enrolled 37 patients. Fifteen patients were treated with tamoxifen 20–40 mg per day for 3–9 months, 10 patients with raloxifene, and 12 patients received no medication. Breast reduction more than 50% was noted in 60% in tamoxifen group and 86% in raloxifene group.

4.5. The surgical management of pediatric gynecomastia

A add up to number of nine articles were gotten, agreeing to the predefined consideration and avoidance criteria, including 479 patients complaining of pediatric and adolescent gynecomastia. Different surgical techniques were described. They were subclassified into two major groups (Fig. 10) (Table 3).

A) The surgical technique included a total of 127 patients, who were eligible for aesthetic excision of the mass through different surgical procedures. The most common surgical procedure used was open subcutaneous mastectomy. Endoscopic assisted adenectomy was tried in 12 patients with highly reported satisfaction rate (92%).
B) The combined surgical excision with liposuction represented the most common technique applied for the management of gynecomastia (352 patients).

Complications were reported in all group with a total number of 83 patients (17.3%). The most commonly complications reported were hypothesia (n = 14), seroma (n = 13) and irregularity (n = 12). On the other hand, surgical site infection and asymmetry were the least reported complications (2 and 4 patients) respectively. Complication rates and distribution are summarised in (Table 2 and Fig. 11). Table 4 described the distribution of complications

Table 1. Obesity and hormonal characteristics in the included studies.

Author, year	Study design	Comparison	Age (years)	N	BMI	Testosterone (pg/dL)	EstradioL (pg/mL)	FSH (mlU/mL)	LH (mlU/mL)	E2/T ratio
Ibrahim et al., 2013[8]	Retrospective cohort	Gynecomastia	12	185	21	1.1	74	1.7	0.5	67.2
		Control	11	357	19	0.9	68	1.4	0.3	75.5
Mieritz et al., 2014[9]	Retrospective cohort	Gynecomastia	12.92	31	19.1	3	30	2.59	2.07	10
		Control	13.14	104	19	3	20	2.18	1.89	6.7
Reinehr et al., 2020[10]	Observational study	Gynecomastia	13.8	86	24.1	1.8	39	ND	3.3	22
		Control	13.7	84	21.3	3.1	41	ND	3.7	18
Kilic et al., 2011[11]	Retrospective cohort	Gynecomastia	13.67	61	23.5	ND	11	2.93	1.80	ND
		Control	13.7	65	18.5	ND	11	3.15	2.15	ND
Dündar et al., 2005[12]	Case-control	Gynecomastia	13.9	20	22.9	1.44	18.5	ND	ND	13.1
		Control	14.2	20	23	1.46	12.1	ND	ND	8.5
ERSOZ et al., 2002[13]	Retrospective cohort	Gynecomastia	19	31	25.18	4.76	29.12	3.75	4.80	6.58
		Control	21	30	21.51	5.70	27.77	2.62	7.32	4.89
Nuzzi et al., 2013[14]	Survey	Gynecomastia	16.51	47	27.02	ND	ND	ND	ND	ND
		Control	16.17	92	23.61	ND	ND	ND	ND	ND
Kulshreshtha et al., 2017[15]	Retrospective cohort	Obese	16.2	54	27.8	2.9	55.7	3.8	3.2	9.13
		Lean	17.1	31	19.9	1.2	64.1	2.9	2.1	6.2
Bitkin et al., 2021[38]	Retrospective analysis	Pubertal Gynecomastia	13.1	36	ND	5.88	12.5	2.91	1.25	2.21
		Pathological Gynecomastia	12.2	7	ND	0.45	20	3.3	1.6	44.4
Lorek et al., 2019[16]	Retrospective analysis	Tanner B = 2	13.6	42	22.4	2.78	23.7	ND	3.5	7.3
		Tanner B > 2	14.1	21	23.3	2.42	26.6	ND	3.2	9.6

per surgical techniques, and showed that the combined mastectomy and liposuction was associated with less complications, compared to the mastectomy technique alone (Fig. 12).

5. Discussion

This think about is the primary efficient audit and meta-analysis designed to comprehensively overview the different etiological, clinical and therapeutic aspects of pediatric and peripupertal gynecomastia.

5.1. Obesity and hormonal dysregulation associated with gynecomastia

Regarding BMI, 8 papers compared gynecomastia to control with a total number of 1724 patients. This meta-analysis revealed that high BMI scores were more significantly associated with gynecomastia. In

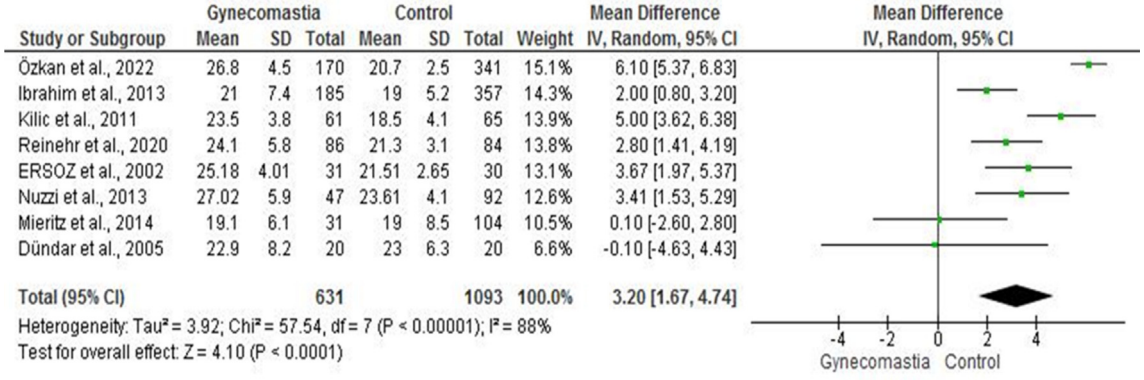

Fig. 3. Forest plot for the changes in BMI.

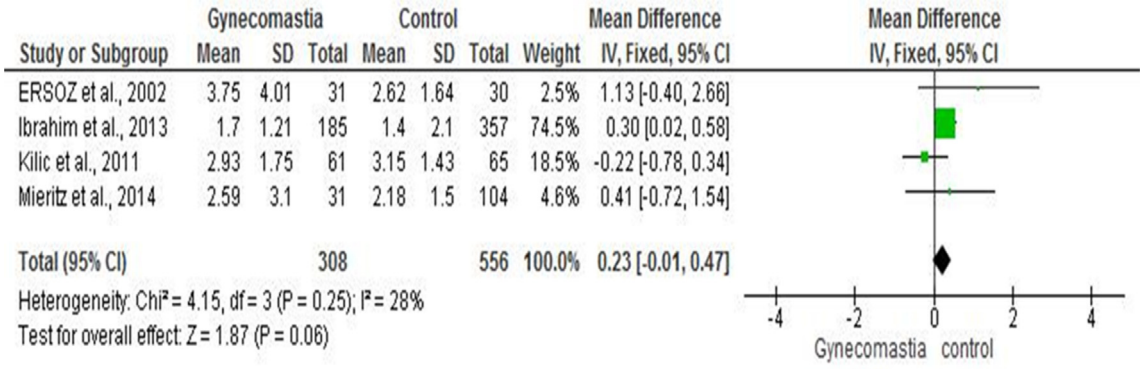

Fig. 4. Forest plot for the changes in testosterone.

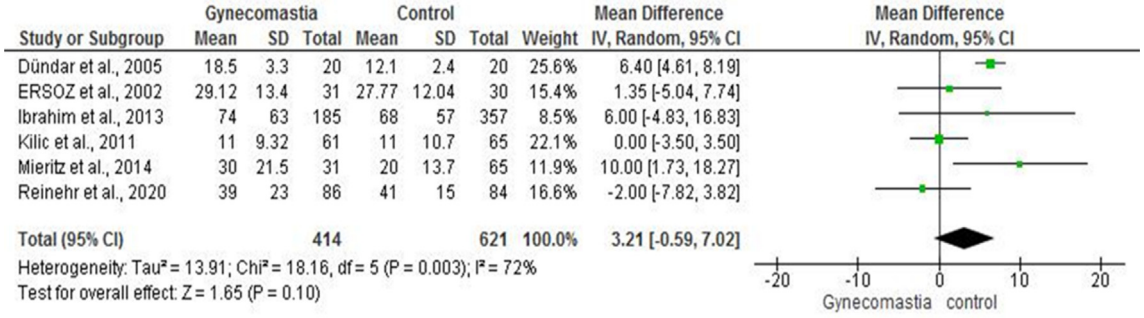

Fig. 5. Forest plot for the changes in Estradiol.

expansion, estradiol (E2) level was higher within the gynecomastia gather, but no factually critical distinction was detailed between the 2 bunches. No critical distinction was detailed between the two think about bunches, regarding the testosterone (T) levels. Although the exact mechanism underlying the development of GM is not well understood yet, an increased estradiol concentration, lagging free testosterone production, and increased tissue sensitivity to normal male levels of estrogen are thought to be the main causes of GM in young boys as reported in **Acharya *et al.***[30] Free testosterone levels in boys with GM have also been shown to be lower than those of without GM According to **Reinehr. *et al.***[10] Moreover, The evidence of a higher prevalence of GM with obesity suggests a probable relation between adipose tissue and GM as reported in **Deberles *et al.***[31]

Fat tissue leads to increased aromatization, and conversion of androgen precursors to estrogen. Consequently, obesity could pose an increased estrogen to androgen ratio According to **Swerdloff, R.**

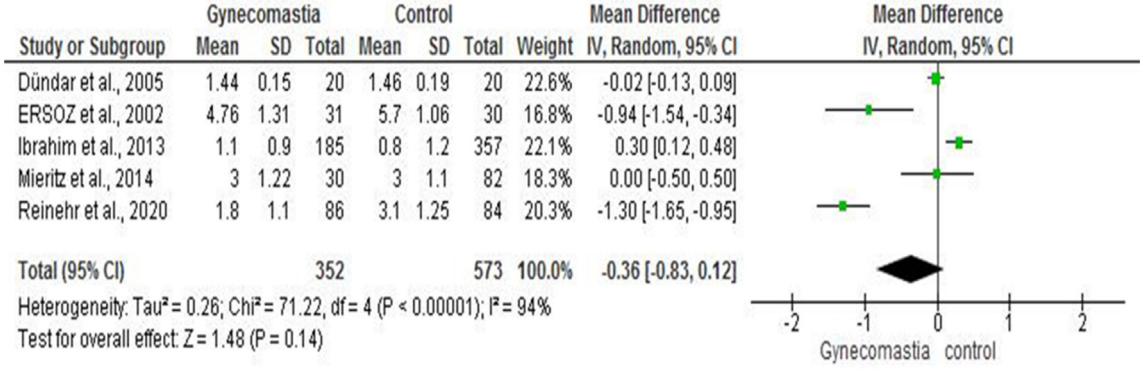

Fig. 6. Forest plot for the changes in FSH.

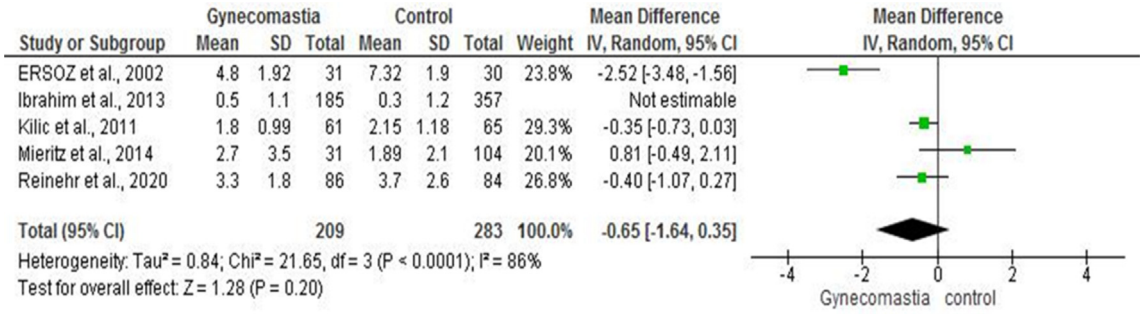

Fig. 7. Forest plot for the changes in LH.

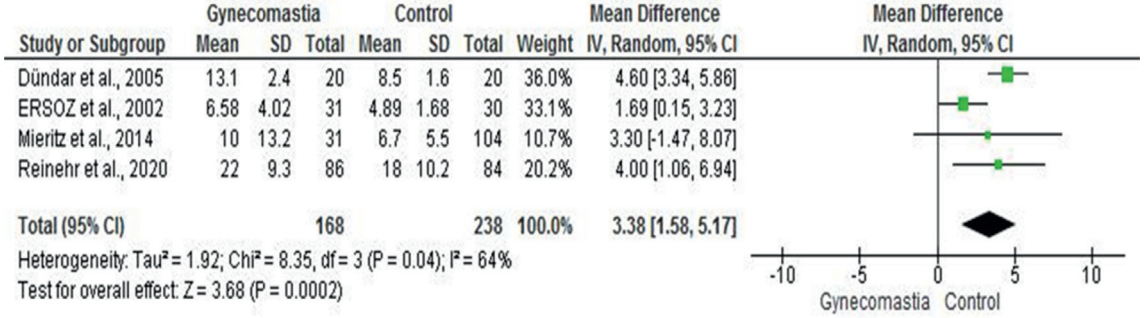

Fig. 8. Forest plot for the changes in E2/T ratio.

S. ***et al.*** Leptin was proposed to straightforwardly invigorate mammary epithelial cells, advance estrogen emission by expanding aromatase action, and/or initiate breast tissue affectability to estrogen as reported in **Braunstein.** ***et al.***[32]

The findings of the present study is in agreement with the study conducted by **Ozkan & Oluklu**, who reported an analysis of the rate of GM and its relationship with nourishment propensities and

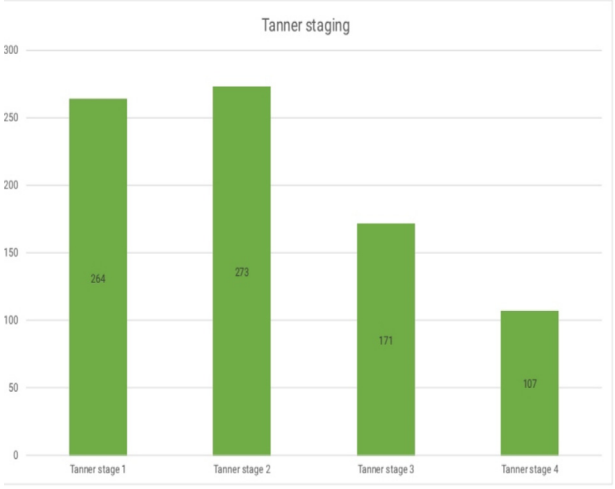

Fig. 9. Tanner staging and classification.

BMI among 511 arbitrarily chosen high-school understudies. They found that BMI was altogether higher in boys with GM compared to the boys without GM. Supportingly, the consider conducted by **Kulshreshtha.** ***et al.*** that assessed the clinical and hormonal profile in 94 adolescent patients with gynecomastia, aged 10–20 years. They found that majority of the patients in the idiopathic GM group were obese (63%) and they had an early onset of GM as compared to lean patients (12.5 years vs. 14.9 years).[15]

Contrary to these reports, **Kumanov. et al**conducted a cross-sectional study on 6200 healthy boys, and reported a negative correlation between GM and BMI.[33]

This meta-analysis revealed that estradiol E2/T testosterone ratio was significantly higher in the gynecomastia group compared to the control group. The cross-sectional study conducted by **Celebi Bitkin.et al** detailed that lopsidedness between estrogen and androgen movement is considered to be mindful for gynecomastia.[24]

5.2. Clinical characteristics and staging of gynecomastia

This study reported that gynecomastia presented bilaterally in the majority of cases (37%), whilst it

Table 2. Clinical characteristics and Tanner staging across the included studies.

Author, year	Unilateral Gynecomastia N (%)	Bilateral Gynecomastia N (%)	Total N	Tanner stage N (%)				Mastalgia N (%)	Obesity N (%)	Swelling N (%)	Psychological disturbance N (%)
				B1	B2	B3	B4				
Acharya et al., 2021[30]	16 (32)	34 (68)	50	0	21 (42)	24 (48)	5 (10)	44 (88)	7 (14)	ND	30 (60)
Bitkin et al., 2021	19 (52.7)	17 (47.3)	36	8 (22.2)	20 (55.5)	3 (8.3)	5 (13.8)	13 (30.2)	ND	ND	ND
Dündar et al., 2005[12]	ND	ND	40	0	17 (42.5)	23 (57.5)	0	ND	ND	ND	ND
Ibrahim et al., 2013[8]	ND	ND	185	68 (36.8)	46 (24.9)	28 (15.1)	23 (12.4)	ND	ND	ND	ND
Kilic et al., 2011[11]	12 (19.7)	49 (80.3)	61	0	12 (19.7)	27 (44.3)	18 (29.5)	36 (59)	ND	61 (100)	15 (24.6)
Lorek et al., 2019[16]	17 (27)	46 (73)	63	0	42 (67)	15 (23.8)	6 (9.5)	ND	7 (11.1)	63 (100)	ND
Mieritz et al., 2014[9]	ND	ND	31	0	8 (25.8)	6 (19.4)	10 (32.3)	ND	ND	ND	ND
Reinehr et al., 2020[10]	38 (30.6)	86 (69.4)	124	ND	ND	ND	ND	ND	52 (42)	ND	ND
ERSOZ et al., 2002[13]	16 (52)	15 (48)	31	ND	ND	ND	ND	16 (52)	ND	ND	ND
Nuzzi et al., 2013[14]	5 (10.6)	42 (89.4)	47	17 (36.2)	12 (25.5)	10 (21.3)	8 (17)	ND	17 (35.2)	ND	47 (100)
Kulshreshtha et al., 2017[15]	15 (18)	70 (82)	85	ND	ND	ND	ND	36 (42)	54 (63.5)	85 (100)	ND
Rosen et al., 2010[29]	7 (10.1)	62 (89.9)	69	ND	ND	ND	ND	11 (15.9)	35 (50.7)	69 (100)	41 (59.4)
Ozkan et al., 2021[17]	ND	ND	170	91 (54)	64 (37)	15 (9)	0	ND	39 (23)	ND	ND
Todorova et al., 2021[39]	ND	ND	110	ND	ND	ND	ND	ND	84 (76.43)	ND	59 (53.5)
Derman et al., 2003[18]	9 (24.3)	28 (75.7)	37	0	6 (16.2)	13 (35.1)	13 (35.1)	6 (16.2)	8 (21.6)	37 (100)	ND

was unilateral in (21%) of cases. Regarding tanner staging, majority of the cases were stage 1 or 2 (66%), stage 1 (32%) and stage 2 (34%). Stage 3 and 4 represented the minority of cases (34%), stage 3 (21%) and stage 4 (13%). In agreement with this study as reported in **Lorek. et al.**[16] found that as it were 19% of patients had intemperate breast estimate. In the study conducted by **Celebi Bitkin. et, al** 20.9% of the patients had over the top breast development, reliable with our findings.[24] Additionally, gynecomastia is as a rule seen reciprocally in 50%–60% of men amid adolescence, and it can be deviated as reported in this study **Johnson.& Murad.**[34] Supportingly, **Celebi Bitkin. et, al** reported that bilateral breast broadening was show in 46.5% of the included patients[24]

5.3. The surgical management of pediatric gynecomastia

Different surgical techniques were described in the present study. The combined surgical excision with liposuction represented the most common technique applied for the management of gynecomastia. Complications were reported in all group with a total prevalence of (17.3%). The most commonly reported complications were hypothesia, seroma and irregularity. On the other hand, surgical site infection and asymmetry were the least reported complications. This study also reported that the combined mastectomy with liposuction was associated with less complications, compared to the mastectomy technique alone. More challenging cases, such as male tuberous breast, can barely be redressed as it were with goal procedures since an

Fig. 10. The rates of surgical techniques application.

Table 3. Demographics and complication rates corresponding to the surgical technique.

Author, year	Age	Intervention	Number	Complications										Satisfaction %
				SSI	HE	SE	ASS	IRR	SC	RET	REC	SENS	Total	
Peters et al., 1998[28]	13–18	Surgical excision (bipedicled flap)	11	0	0	1	0	0	2	0	0	1	4	84
Gabra et al., 2004[23]	9.5–17	Subcutaneous mastectomy	39	1	3	1	0	5	0	1	1	0	12	88
avlin et al., 2017[1]	13–17	combined technique (liposuction + subcutaneous mastectomy)	204	1	0	0	0	0	0	0	0	0	1	ND
Choi et al., 2017[22]	17.5	combined technique (liposuction + subcutaneous mastectomy)	71	0	2	3	0	1	2	2	3	4	17	98.6
Fischer et al., 2014[25]	11–17	combined technique (liposuction + subcutaneous mastectomy)	26	0	1	0	0	1	1	1	1	0	5	88.9
		Subcutaneous mastectomy	11	0	1	0	0	2	0	1	1	0	4	
Laituri et al., 2009[26]	14–18	Subcutaneous mastectomy	12	0	0	1	0	0	0	0	0	0	1	100
		Reduction mammoplasty	8	0	0	0	1	0	0	0	0	0	1	
Varlet et al., 2019[27]	15–18	Endoscopic subcutaneous mastectomy	12	0	0	0	0	0	0	0	0	0	0	92
		Open subcutaneous mastectomy	7	0	0	1	1	1	0	0	0	0	3	
Celebioglu et al., 2004[24]	15–21	Subcutaneous mastectomy	9						1		1	9	11	87
Rosen et al., 2010[29]	12–21	Mastectomy + Liposuction	23		4	6	2	2	4	3	2		23	73.9
		Mastectomy + Liposuction + Mastopexy	21											
		Mastectomy	18											
		Mastectomy + Mastopexy	7											

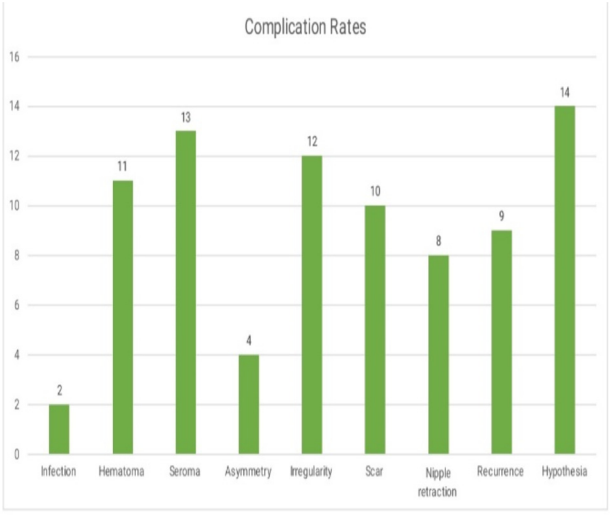

Fig. 11. Distribution of the complication rates.

open extraction is required to oversee the distortion According to **Innocenti.**[35] Open extraction methods base their rule on a coordinate see and administration of the organ, through a few sorts of surgical gets to concurring to the surgeon's inclination and substance of the imperfection as reported in **Innocenti, A., Ghezzi, S.*et al.***[36] The most advantage of open extraction is the coordinate control of the hemostasis and redundant skin control, with the most impediment of changeless scars. Combined methods are as a rule composed of an open extraction stage taken after by an desire stage: the combination of these strategies can allow a restricted scar expansion since, after open extraction, the wide undermining of the skin fold onto a bigger region can ofter allow a adequate skin redistribution as reported in **Mett.** ***et al.***[37]

5.4. Limitations

A few predispositions can be found, for the most part related to the tall varieties in proposed

Table 4. Complication rates per surgical technique.

Complications	Subcutaneous Mastectomy	Combined Liposuction + Subcutaneous Mastectomy
Infection	1	1
Seroma	3	3
Hematoma	4	3
Asymmetry	1	0
Irregularity	8	2
Scar	1	3
Retraction	2	3
Recurrence	3	4
Hypothesia	9	4
Total n (%)	32/39	23/301

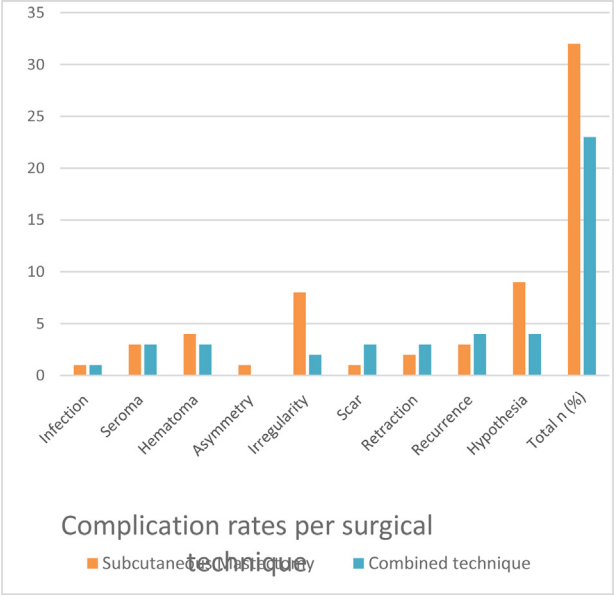

Fig. 12. Complication rates per surgical technique.

medications and clinical classifications. In expansion, no comparison of patients' postoperative fulfillment have been performed since of the nonappearance of assessment in a few papers and for the diverse utilized strategies for assessment. Furthermore, age variation in the included studies is one of the bias sources in this study, as the prevalence of gynecomastia rapidly decline with progression of age. Future randomized control studies are recommended regarding the etiology, medical and surgical intervention by evidence data.

6. Conclusion

This systematic review and meta-analysis investigated the different etiological, clinical and therapeutic aspects of pediatric and peripupertal gynecomastia. Pediatric gynecomastia was significantly more associated with higher BMI and E2/T ratio. Imbalance between estradiol to testosterone levels and the increased sensitivity of estradiol are the main pathological mechanisms, implicated in the development and progression of pediatric gynecomastia. The combined utilization of surgical extraction and liposuction methods appears to diminish the rate of complications compared to surgical extraction alone (Fig. 2).

Authors' contribution

The authors equally contributed in this study.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

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Conflict of Interest

There are no conflicts of interest.

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