Topics in plastic surgery of the breast
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Citation for published version (APA):
Lapid, O. (2014). Topics in plastic surgery of the breast

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TAMOXIFEN THERAPY FOR THE MANAGEMENT OF PUBERTAL GYNECOMASTIA: A SYSTEMATIC REVIEW
ABSTRACT

Objective: A systematic review to assess the efficacy of tamoxifen in the management of idiopathic pubertal gynecomastia.

Data sources: Searches were conducted on the databases of MEDLINE (search engine PubMed) and Web of Science®.

Study selection: Studies reporting the use of tamoxifen for the treatment of gynecomastia in adolescents.

Outcome measure: Resolution of gynecomastia.

Results: A total of 164 publications were found; 59 were selected for retrieval and 6 were included in the review. There were no randomized controlled studies; the studies found have methodological flaws but show promising results. No clinical side-effects were reported or observed.

Conclusion: Tamoxifen may be effective for the treatment of pubertal gynecomastia, and it seems safe to use. Randomized controlled studies are necessary to confirm this indication.
INTRODUCTION
Gynecomastia (GM), breast hypertrophy in men, is common. It is seen in different age
groups with peaks in prevalence postnatally, during puberty and in the elderly [1, 2].
Most cases of GM are idiopathic. Because breast growth is known to be stimulated
by estrogens, an absolute or relative hormonal imbalance is considered by many to
be the main etiology [3]. However, pathological etiologies need to be ruled out; these
include congenital and endocrine disorders, tumors and drugs. In the majority of cases
GM does not require treatment. In cases of idiopathic pubertal GM, reassurance and
an explanation about the natural course of GM is usually sufficient [3]. In all ages if
a specific cause of the GM is diagnosed and treatment is commenced during the
initial phase, the breast enlargement may regress. If GM lasts for over a year, medical
treatment will be unlikely to achieve regression, and surgery may be performed if the
patient requires correction of the GM [4, 5].
It has been suggested that GM may be treated using pharmacological agents.
The rationale behind such therapy is that if GM is caused by a hormonal imbalance,
this may be altered, resulting in regression of the GM. The approaches used are the
administration of exogenous androgens or use of estrogen-receptor blockers that can
mitigate the effect of the surplus of estrogens. The pharmacological agents used from
the first category include testosterone analogues. The drugs of the latter category
include tamoxifen (TMX), an anti-estrogenic non-steroidal drug, and raloxifene. The
use of TMX has received the most attention in the medical literature and was reported
for the treatment of GM as early as 1977 [6]. The use of TMX for GM caused by
the treatment of prostate cancer has been reviewed [7, 8]. However, one cannot
extrapolate from these studies to pubertal GM. We therefore performed a systematic
review in order to assess whether TMX is effective in the management of idiopathic
pubertal GM.

MATERIALS AND METHODS
LITERATURE SEARCH
Citations were retrieved using the terms “Tamoxifen” and “Gynecomastia with the
Boolean operator AND” on 15 April 2013. We conducted the searches, without
language restrictions, in Medline (Search engine: PubMed, all years to April 2013)
which yielded 101 hits, and in Web of Science® (1975 to April 2013) which yielded
128 hits (Figure 1).
The searches were downloaded into Endnote X4 software (Thomson Reuters).
Duplicate records were deleted using the software function, followed by manual
scanning. A total of 164 unique references were found.
The reference lists of the selected publications were screened for additional
publications (by OL), but none was found. The names of the first authors of selected
publications were used for citation tracking (OL & JJvW).
A number of selection criteria had to be met for inclusion.

- Study design: Studies not focusing on idiopathic GM were excluded.
- The age of the participants had to be clearly defined as adolescents aged < 20 years.
- Mixed-age studies were excluded.
- Intervention: Pharmacological intervention with TMX.
- Outcome: Outcome of treatment reported.

The two authors [OL & JJvW] assessed the abstracts of all the studies identified by the initial search and excluded studies that were clearly non-relevant. Full copies of the reports of potentially relevant studies were independently assessed by these two authors using the above-mentioned inclusion criteria. Disagreement on inclusion was
resolved by discussion. An independent third researcher [LP] was available for scrutiny if necessary but was not required.

RESULTS
Six publications met the inclusion criteria. The results of the search are summarized in Table 1.

TYPES OF PARTICIPANT
Alagaratnam presented a case series of 14 participants (adolescents and children at the age of puberty) treated with TMX for 1 to 4 months [9]. No control group was described. König et al. presented experience using TMX in 10 boys with ‘marked pubertal GM’, six of whom had been previously unsuccessfully treated with danazol [10]. No control group was described. Lawrence et al. performed a retrospective chart review of 37 participants with an average age of 14.3 years. Fifteen were treated with TMX, 10 with raloxifene, an estrogen antagonist, and 12 received no medication [11]. The allocation to the different groups was not random; the group that received no medication was not used as a control group and was not followed up. Derman and co-workers published three papers in which the use of TMX for pubertal GM is reported. In the first paper 37 participants aged 10–16 years were treated and followed up for two years [12]. No control group was described. In a second study the effect of TMX on sex hormone-binding globulin in 13 participants and 8 controls was examined [13]. Although the primary goal of the study was to check the effect of TMX on sex hormone-binding globulin, it does offer a control group. The third publication by Derman et al. describes the long-term follow up of 10 participants treated with TMX and followed for 2.5–7 years [14]. This study suffers from a loss to follow up of 44% of the eligible patients. The first author of these studies was contacted to ascertain that there was no overlap of the patients in these three studies.

TYPES OF INTERVENTION
Different interventions were reported: Alagaratnam treated the patients for 1–4 months but did not mention the dosage of the TMX prescribed [9]. König et al. prescribed 20–40 mg TMX per day for periods between 2 and 12 months [10]. Lawrence et al. used 10 or 20 mg TMX twice daily for 3–9 months [11]. Derman and co-workers in all three studies used dosages of 10 or 20 mg TMX twice a day for periods between 2 and 12 months [12-14]. In all the studies that specified the dosage it was adjusted according to the response. The length of the therapy was also dependent on the response.

TYPES OF OUTCOME MEASURE
The studies used different measures to define the outcome: Alagaratnam reported the size range of the GM before treatment and reported as an outcome ‘complete regression’. Although this was observed in 12 patients (86%), 2 of the patients relapsed [9]. König et al. reported the change in the diameter of the breast. Eight of
Table 1. Summary of the publications included in the review

<table>
<thead>
<tr>
<th>Publication</th>
<th>Design</th>
<th>Population</th>
<th>Intervention</th>
<th>Control</th>
<th>F/U</th>
<th>Pain resolution</th>
<th>Swelling reduction rate</th>
<th>Recurrence rate</th>
<th>Side-effects</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alagaratnam, 1987</td>
<td>Retrospective</td>
<td>14 adolescents</td>
<td>Dose – NS for 1-4 mo (2.4)</td>
<td>None</td>
<td>18 mo</td>
<td>–</td>
<td>86%</td>
<td>14%</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Derman et al. 2003</td>
<td>Case series</td>
<td>37 patients aged 10–16 (13.8)</td>
<td>10 or 20 mg bid for 2-8 mo</td>
<td>None</td>
<td>2 yr</td>
<td>100% of 7 patients with pain</td>
<td>95%</td>
<td>5%</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Derman et al. 2004</td>
<td>Case series</td>
<td>13 patients aged 10–15.8</td>
<td>10 or 20 mg bid for up to 8 mo</td>
<td>No therapy in 8 patients</td>
<td>4–40 mo (21)</td>
<td>–</td>
<td>TMX 100% Control 75%</td>
<td>–</td>
<td>None</td>
<td>Control allocation not specified</td>
</tr>
<tr>
<td>Derman et al. 2008</td>
<td>Prospective</td>
<td>10 patients aged 11.5–14 (12.7)</td>
<td>10 or 20 mg bid for 3–8 mo (5.7)</td>
<td>None</td>
<td>2.5–7 yr</td>
<td>–</td>
<td>90</td>
<td>0</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>König et al. 1987</td>
<td>Case series</td>
<td>10 patients aged 13–18.8</td>
<td>20–40 mg per day for 2–12 mo (5.5)</td>
<td>–</td>
<td>–</td>
<td>80</td>
<td>–</td>
<td>–</td>
<td>None</td>
<td>6 patients previously treated with danazol</td>
</tr>
<tr>
<td>Lawrence et al. 2004</td>
<td>Retrospective</td>
<td>15 patients aged 12–16.6</td>
<td>10 or 20 mg bid for 3–9 mo (5.1)</td>
<td>13 patients no treatment</td>
<td>3 yr</td>
<td>TMX 91% Ralofixene 86%</td>
<td>0% but 40% of patients went on to surgery</td>
<td>None</td>
<td>Control allocation not specified</td>
<td></td>
</tr>
</tbody>
</table>

**Remarks:** None
the 10 participants had full resolution and 2 had partial resolution of their GM [10]. Lawrence et al. measured the diameter of the breast tissue by palpation. Twenty out of 22 breasts (86%) treated with TMX had a decrease in size. However, a decrease of more than 50% in the size of the nodule, which was considered a response, was seen only in nine patients. The percentages for the group treated with raloxifene were 86% decrease in size and 86% response [11]. Derman and co-workers used the same outcome measure in all three studies, namely measuring the widest diameter of the swelling with tape. In the first study disappearance of breast swelling was used as the outcome and occurred in all patients. Pain was recorded as having disappeared within one month in 33 patients and in the remaining 4 patients within 2 months [12]. In their second study similar methods were used to measure the breasts. The successful effect of TMX was defined as reduction in size and this was seen in 12 of the 13 patients. This study includes reporting of the size in the different patients. However, only in 2 patients was the GM not detectable following treatment. In the control group which had smaller breast enlargements, 7 of the 8 patients had a decrease in size [13]. In the third report of the same group with long-term follow up only one patient had palpable breast tissue 1x1 and 0.5x 0.5 cm [14].

SIDE-EFFECTS
No clinical side-effects were reported by any of the studies. König et al. however, found an increase in the testosterone and estradiol levels in the blood of the participants and an increase in sex hormone-binding protein in the 4 patients in which it was measured [10]. The effect of TMX on sex hormone-binding globulin was studied by Derman et al. They concluded that the pubertal fall in sex hormone-binding globulin levels is attenuated by TMX. They did not find any decreased statural growth in any patient [13].

DISCUSSION
Pubertal GM, although often considered a normal finding, can be a cause of distress and discomfort. Adolescents seeking treatment are usually offered reassurances or surgery. The use of TMX is an option that is mentioned in various review papers [2, 3]. Using medicine seems like a logical approach and is less invasive and less costly than surgery. A recent systematic review by Kunath et al. suggested that TMX is effective for the prevention and treatment of GM induced by non-steroidal anti-androgens [7]. We therefore decided to perform our own systematic review to assess the evidence for the use of TMX in treating pubertal GM.

We found no randomized controlled studies on the use of TMX for the treatment of pubertal GM. Most of the papers reviewed were case reports, review articles and opinions discussing or mentioning the use of TMX. These papers often quoted previous publications with a low level of evidence, giving the false impression that there is good evidence for this practice. Other papers referred to the use of TMX
in adults or included mixed groups. In the older age groups the etiology was often mixed, thus not only idiopathic, and often associated with the medical treatment of prostate cancer. Such papers supporting the use of TMX were not included due to the fact that they were beyond the scope of this systematic review.

One of the studies we had to exclude reported complete resolution in 97 of 98 cases of pubertal GM. However, only 89 were idiopathic, the rest being diagnosed with hyperprolactinemia and thyroid problems. We therefore elected not to include this study. In addition, this paper lacks data on the severity of the findings and the precise outcome measures used [15].

The level of evidence of the six studies that met the search criteria is low [16]. None of the studies were randomized controlled studies, and the studies that did have controls had no randomization [11, 13]. In one of those studies, it is reported that there was a difference in the severity of GM between the two groups and it can therefore only be seen as a case series like the rest of the studies [13]. The lack of controlled studies is of great concern, since pubertal GM is often a self-limiting process in which we expect a spontaneous resolution in a substantial percentage of the patients [17].

A further problem in the included studies is the lack of uniformity in assessing the severity of the GM and in defining the outcome and effectiveness of the treatment. There have been severity scales reported for GM but they were not used in all the studies. Also, measuring the GM using calipers or a tape may be imprecise and dependent on the examiner, and none of the reports referred to intra- or inter-rater reliability. Pain, which is easier to define, was used as a measure in only one paper but the commonly accepted visual analogue scale was not used [12].

None of the studies found that TMX had serious side-effects. Derman reported that there was no effect on the growth of the patients and that they reached heights similar to the predicted values [14]. This is similar to the findings reported by Kreher et al. who used TMX in order to delay bone maturation and improve height potential in short pubertal boys [18].

It is important to note that the use of TMX for GM is off-label. It is even more difficult to justify its use in idiopathic pubertal GM without having results available of the impact of TMX therapy on long-term adverse events and on physical as well as mental development.

CONCLUSION

Although TMX therapy for pubertal GM might be safe and effective, the available evidence in the medical literature is insufficient to prove this. For proof a well-conducted, randomized and controlled study would be necessary. As the base of evidence is currently low, the off-label indication for prescribing TMX for GM should be emphasized to patients and their caregivers.
REFERENCES


