ORIGINAL ARTICLE

Gestational Gigantomastia: A Systematic Review of Case Reports

Mishu Mangla, Deepak Singla[1]

Department of Gynecology and Obstetrics, Himalayan Institute of Medical Sciences, Dehradun, [1]Department of Anesthesia, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India

ABSTRACT

Introduction: Gestational gigantomastia (GG) is a rare disease characterized by diffuse, extreme, and incapacitating enlargement of one or both breasts during pregnancy. Although benign, it can lead to a great social, emotional, and physical disability. A good and complete knowledge regarding this rare but distressing clinical situation is a must among all practicing physicians especially obstetricians.
Materials and Methods: A systematic review of all the case reports and short case series, published in the English language in various databases in the last 40 years, i.e. 1976 to 2016 was carried out. The main aim was to provide a summary and critical analysis of all the data and evidence regarding GG published in recent years.
Results: After considering all inclusion and exclusion criteria, a total of fifty case reports were finally analyzed. The risk factors, geographical distribution, associated diseases, and the main treatment modalities used for GG are discussed in detail in this article.
Conclusion: Multidisciplinary team effort in the form of obstetrician, plastic surgeon and anesthetist, and pediatrician is required for a successful fetomaternal outcome.

Key Words: Breast diseases, gestational, gigantomastia, macromastia, pregnancy

INTRODUCTION

Gestational gigantomastia (GG) or gravidic macromastia is defined as a disorder characterized by a diffuse, extreme and incapacitating enlargement of one or both breast during pregnancy.[1] It has an incidence ranging from 1 in 28,000 to 1 in 100,000 pregnancies worldwide.[2] The credit of reporting the first case of GG in medical literature has been given to Palmuth.[3] The definition of this rare disease is although not clear, Lewison *et al.* used beautiful words to describe a typical case "True gigantomastia develops rapidly during pregnancy, undergoes regression after delivery, and recurs with subsequent pregnancies."[4] Although only rare cases have been reported in literature that underwent complete spontaneous resolution after pregnancy, majority of cases need either medical or surgical treatment. Apart from being a social and emotional disability, it can lead to a myriad of physical symptoms as well, which include breast pain, infection, ulceration, postural problems and back pain. It can even lead to chronic traction and thereby causing temporary or permanent damage to fourth, fifth, or sixth intercostals nerves presenting in the form of loss of nipple sensation, further promoting infection and ulceration.[2] It is a much bigger problem in developing countries where the importance of breastfeeding for the newborn child cannot be underrated, and this problem *per se* by its very presence hinders with it totally. The main aim of this systematic review was to provide a summary and critical analysis of all data and evidence regarding GG published in recent years

Address for Correspondence: Dr. Mishu Mangla, Department of Gynecology and Obstetrics, Himalayan Institute of Medical Sciences, Jolly Grant, Dehradun, India.
E-mail: deepak10.4u@gmail.com

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from worldwide. Since this data are mainly in the form of case reports and short case series, a systematic analysis of case reports was undertaken. Knowledge regarding this rare but debilitating disease is a must among all practicing physicians especially obstetricians and gynecologists because that is where a patient with GG usually first approaches.

MATERIALS AND METHODS

An electronic search of PubMed, EMBASE, and Scopus and other databases was carried out for case reports and short case series on GG, published in English from 1976 to 2016, i.e., the past 40 years. The electronic search strategy was done using keywords as "pregnancy" and "gigantomastia" "gestational" and "gigantomastia" "gestational" and "macromastia," "gestational" and "mammary hyperplasia" and "gravidic" and "macromastia." The author independently analyzed the title and abstracts of all case reports found from the initial search. The data thus extracted were double checked to avoid any duplication.

This systematic review was planned according to PRISMA guidelines. To be included in the present review, the article had to pertain only to excessive enlargement of breast in pregnancy. All case reports, in which either the author had reported the enlargement of breast in the patient being noted before pregnancy, cases relating to puberty-related gigantomastia or cases relating to drug-related gigantomastia were excluded from the study. Any article that was not a case report or short case series, i.e. review articles, original articles, clinical trial, or commentary was also excluded from the present systematic review.

Data were extracted from all the case reports or short case series finally included in the systematic review and entered into Excel sheet. The data extracted included geographical distribution or country of occurrence of the case, year of publication, age of the patient at the time of presentation, gravidity, and the duration of pregnancy in weeks or the trimester, in which the onset of GG was seen. Whether GG was unilateral or bilateral, was it recurrent with successive pregnancies or not was any other medical disease associated with it or not was also noted. Finally, a note was also made of the management strategy used for the case.

Descriptive statistics was used to calculate simple frequency, percentage, and proportion out of the total case reports.

RESULTS

A total of 281 case reports were found on electronic data search of PubMed, EMBASE, Scopus database, and through other sources from 1976 to 2016. After removing the duplicates and case reports on nonhuman subjects, we were left with a total of 238 articles. One hundred and eighty-eight articles were excluded as they were relating to either pubertal gigantomastia, drug-related gigantomastia, or other causes of gigantomastia but unrelated to pregnancy or were in any other language apart from English. Considering all the inclusion and exclusion criteria, a total of 50 case reports were finally analyzed [Figure 1].

Cases have been reported from worldwide. The geographical distribution of the cases has been shown in Figure 2. Although no specific area predominance was found, 11 cases each have been reported from Europe and North America, eight cases from South East Asia, seven from Central Asia, and six from Africa. The distribution of articles according to the year of publication has been shown in Figure 3. It is interesting to note that the number of cases being reported has increased significantly from the year 2000 onward.

Age of the patients, in whom GG has been reported, varied from 16 to 35 years, with the majority of cases reported from 26 to 30 years of age (21/50). In one of the reported cases, the age of the patient was not known. 29/50 cases had their onset in the first trimester, 14/50 cases were reported to develop during the second trimester, and 2/50 in the third trimester. Interestingly, one case has been reported, in which GG developed in the postpartum period. The time of onset of GG was not known in four case reports [Figure 4]. Majority of cases (46/50) of GG were bilateral. Only four cases of unilateral GG were found during the study. Although no associated systemic medical disease was found in the majority of patients with GG, 4/50 patients had coexistent myasthenia gravis, 3/50 had lymphoma (two had non-Hodgkin's lymphoma, and 1 had T-cell lymphoblastic lymphoma), 2/50 had antiphospholipid antibody syndrome, and 1/50 had mirror syndrome. 2/50 patients with GG developed hypercalcemia due to pseudohyperparathyroidism as a paraneoplastic syndrome.

Different authors have used different treatment strategies for the management of GG [Figure 5]. Only two cases underwent spontaneous resolution in the postpartum period and did not need any specific treatment. Supportive and conservative management was done in 3/50 cases, local debridement with bromocriptine in 4/50 patients and only medical treatment in the form of bromocriptine in 2/50 cases, which was the main treatment modality. Reduction mammoplasty (22/50) and simple mastectomy (15/50) were the two most commonly and successfully used treatment strategies for GG. One of the case reports introduced bilateral subcutaneous mastectomy with latissimus dorsi flap as a new technique for treatment. In two of the case reports analyzed the authors had not mentioned clearly regarding the treatment strategy they used.

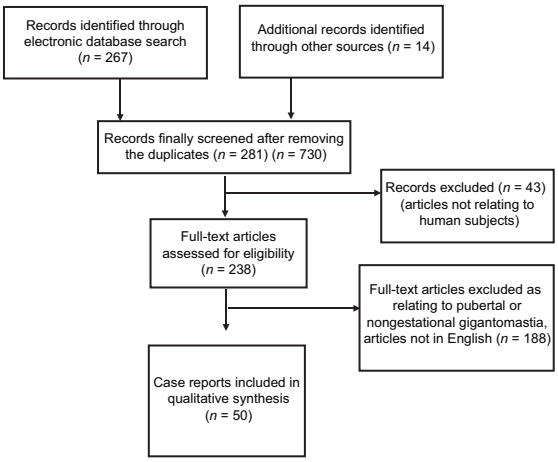

Figure 1: PRISMA flow chart of the screening process

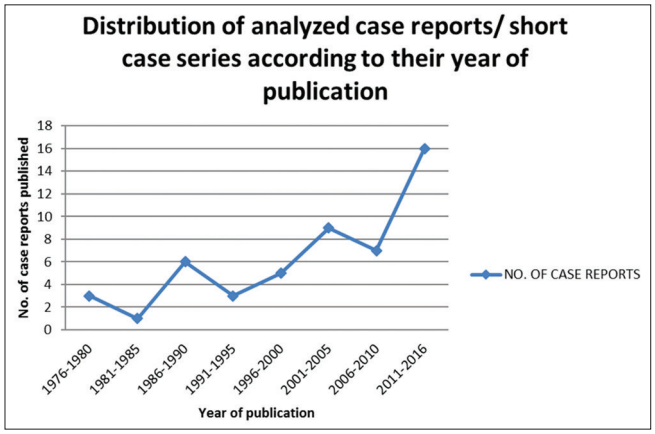

Figure 3: Temporal distribution of the case reports according to year of publication

DISCUSSION

There is still no universally accepted definition of GG. It is defined as rapid and disproportionate growth of breast during pregnancy.[5] Another more discrete definition used is an enlargement of breast, where more than 1500 g of breast tissue needs to be removed from the breast.[2] Although an incidence of 1:28,000-1:100,000 has been reported in the past, this may not be exact as this obviously suffers from observer bias as many cases considered to be "within the norm" as said by Lapid may actually be GG.[5]

Only the cases of GG published in the past 50 years have been included in the present review. First, the treatment modalities that were followed in the past may not be very relevant in the present scenario, as medicine is an ever-evolving branch. In the past, the management was mainly conservative, but in today's world, both anesthesia and plastic surgery are safe even during pregnancy. Thus, surgery is the mainstay of treatment. Second, many authors in the past even used to recommend elective termination of pregnancy in patients with GG, this is definitely not

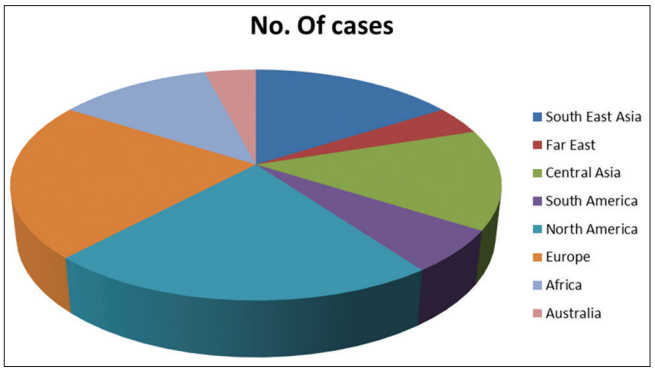

Figure 2: Geographical distribution of the reported cases of gestational gigantomastia in the last 40 years

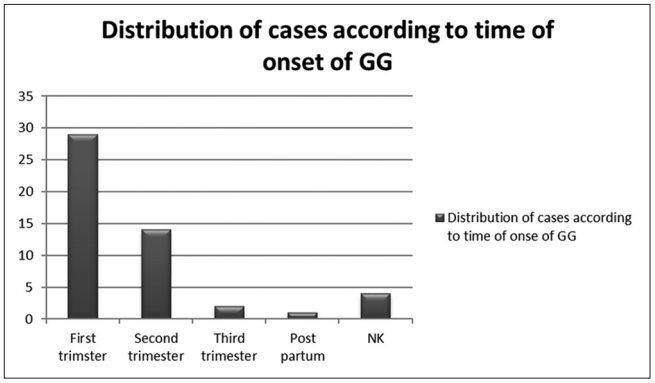

Figure 4: Onset of gestational gigantomastia in pregnancy

relevant in the present day world where every pregnancy is taken up to be a precious pregnancy, and there are many patients who may have conceived after long treatments of infertility and this could even be their last chance of achieving a successful pregnancy outcome.

GG is a rare disease. Although the natural history of the disease has not been clearly elucidated, a number of plausible explanations have been given in the past. The risk factors are not fully defined. However, it has been reported to be more common in Caucasian women in comparison to African-American women (9:4).[6] It has been found to be more common in multiparous, but maternal age and fetal gender do not seem to have any significant association.[1] Although it can occur in any pregnancy, the occurrence of GG in one pregnancy is probably the strongest risk factor for its recurrence in subsequent pregnancies.[7-9] One significant risk factor which has not received much attention in the past is the concurrent presence of other autoimmune diseases. It is more common in patients with autoimmune conditions such as myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis or autoimmune thyroiditis. This is supported by a study conducted by Touraine *et al.* in a series of eight patients in whom they studied gigantomastia in context of autoimmune diseases.[10] The exact etiopathology of GG has not been established. Many possible theories

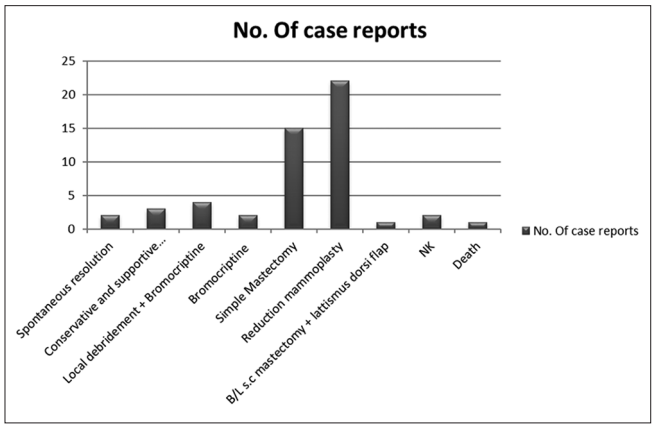

Figure 5: Treatment modalities used for gestational gigantomastia in the cases reported in the last 40 years

have been postulated in the past, but none of these has received widespread acceptance. Some of these include hormone receptor hypersensitivity,[4] impaired liver function or steroid metabolism,[4] high serum prolactin,[6] malignancy,[11] or even autoimmune diseases.[10]

Majority of cases of GG are bilateral and have their onset in the first or early second trimester [Figure 4]. The reason for this predominance is although not clear, this period coincides with the period of peak gonadotropin production during pregnancy, further strengthening the hypothesis of hormonal association.[12] Some cases may have abnormal hormonal milieu; but in majority of cases, the level of hormones, estrogen, progesterone, and prolactin is within normal limits. Then, what causes unilateral enlargement of breast in some cases is still a dilemma.[7,13-15] Interestingly, in one of the cases of GG reported from Japan, the level of CA 19.9 was found to be elevated significantly.[7]

Although the condition is completely benign, the clinical presentation may mimick malignancy, on the one hand, due to rapid enlargement in the size of the breast and on the other hand, due to edema of the underlying tissue, which can give peau-d-orange appearance. Bilateral axillary swelling due to similar hypertrophy of the accessory axillary breast tissue may be confused with lymphadenopathy of malignancy.[16] However, underlying malignancy should always be kept in mind and excluded first as there have been case reports, in which patients initially presenting with GG later proved to have underlying malignancy.[11,14,17]

GG, although benign, can be a great emotional, physical, and social disability for a woman. It can lead to a myriad of complications for both the mother and the fetus. There can be skin ulceration, necrosis, infection, shoulder and back pain, and even postural instability. Lymphatic and venous stasis can further predispose to the development of ulcers. Severe sepsis, renal dysfunction, multiorgan dysfunction syndrome, and even death have been reported in rare patients with GG.[18] There have even been reports of two peripartum fetal deaths although we could not find any such case in the past 40 years. However, elective termination of pregnancy, even with a previable fetus may become necessary if the maternal condition demands so.

Treatment of GG still remains largely controversial. The main reason could be because the exact etiopathology of this rare disease is still not completely understood. Second, it may be a common manifestation of an array of systemic manifestations in the body in the form of auto immune diseases or even malignant disease as in cases of non-Hodgkin's lymphoma. Although medical management is the first line of treatment, surgery is the mainstay. With advances in both surgery and anesthesia, surgery probably at any gestational age is safe nowadays. Elective pregnancy termination as a treatment of GG is no longer recommended as not only is this ethically unacceptable but it also does not guarantee cure.

Bromocriptine has been the mainstay of medical management in patients with GG. It is an ergot derivative, a dopamine D2 receptor agonist with both agonist and antagonistic properties on D1 receptors. It has been found to be safe during pregnancy as the incidence of abortions, ectopic pregnancy, and congenital malformations in women taking bromocriptine even in early pregnancy have not been found to significantly different than that in nonusers.[19] Although no major side effects have been reported but some isolated case reports suggest intrauterine growth retardation as an isolated side effect.[20] Hence, it is recommended that serial fetal growth monitoring should be done in patients on bromocriptine for gigantomastia. Although our extensive data search also showed only two cases of GG that were successfully managed with bromocriptine alone, Swelstad *et al.* in their literature search also found variable results with bromocriptine. It definitely has a role to arrest further growth and hyperplasia of the mammary tissue but whether it causes regression of gigantomastia or not proved. Numerous other drugs, 2 Br-alpha ergocryptine,[21] androgens, estrogens, and progesterone have also been tried but with limited success.[4,22-24] Norethindrone, stilbesterol, and tamoxifen have also been used but all in vain.[4,25]

Although a trial of medical treatment should be given in all patients, surgery is the mainstay of treatment. Since these patients are at a high risk of preterm labor and induced preterm delivery, an effort should be made to postpone the surgery to a stage at which a viable fetus with mature lungs can be delivered.[5] Corticosteroids may be needed for lung maturity in case the delivery of a premature fetus is indicated or planned. Two main surgical modalities that have been widely used in the treatment are

reduction mammoplasty and total mastectomy. Although breast reduction reduces the total amount of breast tissue in the existing scenario and may offer an advantage of postoperative breastfeeding function of the breast, the main disadvantage of this procedure is that even the small amount of breast tissue that is left behind can undergo significant hyperplasia in next pregnancy to present again as gigantomastia. Obviously, bilateral mastectomy with delayed reconstruction would have this advantage of less chances of recurrence, especially in cases, in which the patient is desirous of future pregnancies.[26] Various techniques of breast reconstruction have been described by many authors[22,26-28] and are mainly of concern to plastic surgery, so would not be discussed in detail here.

An attempt has been made to summarize all recent published data and evidence regarding GG. The present article, however, has certain limitations. First, only the data published in the last 40 years was included in this study; this could have led to missing out on interesting and unusual cases. Second, the author cannot deny the possibility of missing out rare published cases that were either not traced in the above-mentioned electronic search. More studies, probably at the molecular level are needed to find out the exact etiology of this rare but debilitating disease so as to find a treatment that can arrest the progress at an early stage.

CONCLUSION

A good and complete knowledge regarding this rare but distressing clinical situation is a must among all practicing physicians especially obstetricians. Multidisciplinary team effort in the form of obstetrician, plastic surgeon and anesthetist, and pediatrician is required for a successful fetomaternal outcome.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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