



EVIDENCE SEARCH RESULTS

Question/subject of request:	in women with a diagnosis of otosclerosis - does exogenous oestrogen influence disease progression compared to women not exposed to exogenous oestrogen - does exogenous progesterone influence disease progression compared to women not exposed to exogenous progesterone
Date requested:	2 Jan 2025
Date completed:	6 Jan 2025
Compiled by:	Roxanne Hart

CITING THIS SEARCH

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The citation format is:

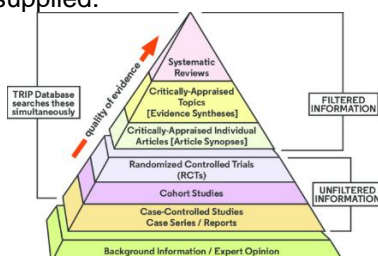
- Hart, R., (2024). *Evidence summary:exogenous oestrogen and otosclerosis* Taunton, UK: Somerset Foundation Trust Knowledge and Library Services.

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The results are presented according to the hierarchy of evidence which is used to rank the relative strength of results obtained from scientific research.

The design of the study and the endpoints measured affect the strength of the evidence.

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Summary of search results:

There is very little written on this topic, for this reason I included older research including back to 2001. Although the request form stipulated no summary or synthesis I have grouped the research by theme which can be seen above in the contents section.



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Thank you.





Pregnancy

Macielak, R. J., Marinelli, J. P., Totten, D. J., Lohse, C. M., Grossardt, B. R., & Carlson, M. L. (2021). [Pregnancy, estrogen exposure, and the development of otosclerosis: A case-control study of 1196 women](#). *Otolaryngology - Head & Neck Surgery*, 164(6), 1294-1298.

OBJECTIVE: This study sought to determine whether a history of pregnancy or bilateral oophorectomy is associated with subsequent otosclerosis development or disease severity. **STUDY DESIGN:** Population-based case-control study. **SETTING:** Olmsted County, Minnesota. **METHODS:** Women diagnosed with otosclerosis were matched to 3 women without otosclerosis based on age and historical depth of medical records. Associations of prior delivery and bilateral oophorectomy with subsequent development of otosclerosis and with pure-tone average (PTA) at the time of otosclerosis diagnosis were evaluated. **RESULTS:** We studied 1196 women: 299 cases of otosclerosis and 897 matched controls. The odds ratio for the association of ≥ 1 delivery with otosclerosis was 1.16 (95% confidence interval [CI] 0.85-1.60; $P = .35$). Odds ratios for the associations of 1, 2, 3, or ≥ 4 deliveries with otosclerosis were 1.22 (0.83-1.80), 1.09 (0.71-1.68), 1.28 (0.77-2.12), and 1.00 (0.54-1.84), respectively. The odds ratio for the association of prior bilateral oophorectomy with otosclerosis was 1.12 (0.58-2.18; $P = .73$). In cases with otosclerosis, PTA at diagnosis was not significantly higher for women with ≥ 1 delivery as compared with those without (median 45 dB hearing loss [HL] [interquartile range {IQR} 36-55] vs 43 [IQR 34-53]; $P = 0.18$) but was significantly higher for women with bilateral oophorectomy compared with those without (median 54 dB HL [IQR 44-61] vs 44 [IQR 34-53]; $P = .03$). **CONCLUSION:** These data do not support a relationship between endogenous estrogen exposure and development of otosclerosis. Women with otosclerosis who had a history of pregnancy did not have significantly worse hearing at the time of diagnosis, suggesting that pregnancy is not associated with disease severity.

Qian, Z. J., & Alyono, J. C. (2020). [Effects of pregnancy on otosclerosis](#). *Otolaryngology-Head and Neck Surgery*, 162(4), 544-547.

Objective: The effect of pregnancy on otosclerosis is controversial. If pregnancy physiologically increases the risk of progression, females with children would be expected to receive stapedectomy earlier than childless females and males. Here, we seek to determine whether sex moderates the relationship between number of children and age at stapedectomy.

Study design: Retrospective observational study of national health care claims.

Setting: 2003 to 2016 Optum Clinformatics Data Mart.

Subjects and methods: In total, 6025 privately insured US adults (3553 females, 2472 males) who received stapedectomy for otosclerosis were queried for age and number of children at the time of initial surgery.

Results: The average age at stapedectomy was significantly lower in females than males (46.8 vs 48.1 years; t test, $P < .0001$). Females with children had a significantly lower age at surgery compared to childless females (39.3 vs 49.9 years; t test, $P < .0001$). Males with children similarly had a significantly lower age at surgery compared to childless males (40.5 vs 51.3 years; t test, $P < .0001$). A higher number of children was correlated with lower age for both females (Pearson, $r = -0.3817$, $P < .0001$) and males (Pearson, $r = -0.3675$, $P < .0001$). Linear regression showed that younger age of surgery could be predicted by female sex and number of children ($F(3, 6021) = 336.93$, $P < .001$, $R^2 = 0.1437$) with no significant interaction between sex and number of children ($P = .186$).





Conclusion: Sex does not moderate the effect of increasing number of children on decreasing age at stapedectomy. Social, rather than biological, factors surrounding parenthood such as increased overall health care utilization may explain prior associations between pregnancy and otosclerosis.

Crompton, M., Cadge, B. A., Ziff, J. L., Mowat, A. J., Nash, R., Lavy, J. A., ... & Dawson, S. J. (2019). [The epidemiology of otosclerosis in a British cohort.](#) *Otology & Neurotology*, 40(1), 22-30.

Objective: To analyse the epidemiology of otosclerosis in a British cohort collected between 2011 and 2017.

Design: Retrospective cohort study.

Setting: Five UK ENT Departments.

Patients: Patients with surgically confirmed otosclerosis.

Main outcome measures: Questionnaire data documented family history of otosclerosis, age of onset, medical history, and information on associated risk factors for 657 patients. Pre and post-surgical pure-tone audiometry was collected for 154 of these patients.

Results: The age of onset, incidence of bilateral disease, tinnitus and vertigo, a higher prevalence of women (65%) than men (35%) are similar to those reported previously for otosclerosis cohorts. No association with measles infection was detected. Patients with a family history (40%) have an earlier age of onset and a higher incidence of bilateral disease and vertigo than non-familial subjects. Pedigree analysis is consistent with an autosomal dominant inheritance with reduced penetrance being apparent in 44/91 pedigrees studied. Women who associate their hearing loss with pregnancy have an earlier age of onset than those that do not ($p = 6 \times 10^{-6}$).

Conclusions: This study confirms that otosclerosis is an early adult onset disease that is more prevalent in women than men with a large minority of patients having a family history of otosclerosis. We report new evidence to support a relationship between pregnancy and otosclerosis progression in a proportion of women. In addition, this is the first study to identify differences in severity between familial and non-familial cases of otosclerosis, highlighting the possibility that more than one etiology may be involved.

Fabbris, C., Moltteni, G., Tommasi, N., & Marchioni, D. (2022). [Does pregnancy have an influence on otosclerosis?](#) *The Journal of Laryngology & Otology*, 136(3), 191-196.

OBJECTIVE: Otosclerosis affects women twice as often as men, especially during fertile age. A role of female hormones has been claimed, but controversy still exists regarding the influence of pregnancy. The purpose of this research was to analyse the role of pregnancy on the course of otosclerosis.

METHOD(S): PubMed was searched in May 2019 using the terms 'otosclerosis AND pregnancy', 'otosclerosis AND pregnant', 'otosclerosis AND parous', 'otosclerosis AND parity', and 'otosclerosis AND puerperium'. Age at diagnosis, number of pregnancies and the temporal relationship of the disease with childbearing were considered.

RESULT(S): From 65 articles, 11 were chosen for review. They described 2323 women affected by otosclerosis: 1805 had at least 1 pregnancy, while 518 did not. During childbearing, otosclerosis began in 1 per cent of pregnant women, worsened in 21 per cent and worsened during puerperium in 4 per cent. Often, the authors reported hearing change with pregnancy without details, so a further group has been considered composed of women belonging to any of the groups just mentioned or to another group of women not further characterised. Overall, hearing change occurred during pregnancy in 44 per cent. A statistically significant correlation emerged between hearing change and number of pregnancies ($p = 0.003$).

CONCLUSION(S): Because of wide data heterogeneity and the difficulty in analysing a single





factor, absolute statements could not be formulated. According to this review, pregnancy seems to have a worsening effect on the course of otosclerosis.

Oral contraception

Vessey M, Painter R: Oral contraception and ear disease: findings in a large cohort study. *Contraception* 2001;63:61–63. For a copy of the full text please email library@somersetft.nhs.uk

A number of authors have suggested that oral contraceptives may increase the risk of certain ear diseases, especially otosclerosis and vestibular disorders, although the amount of published information on this topic is limited. We have analyzed the available data on ear disease in the Oxford-Family Planning Association contraceptive study that includes 17,032 women followed for periods of up to 26 years. No evidence of any adverse effect of oral contraceptives on ear disease was detected. A protective effect of oral contraceptives against wax in the ear has been described in the Royal College of General Practitioners oral contraception study. The amount of data available in the Oxford-Family Planning Association study was too small to permit confirmation or refutation of this finding.

Niedermeyer, H. P. (2009). [[Ingestion of oral contraceptives with a family history of otosclerosis.](#)] *Internistische Praxis*, 49(1), 101–102.

Thys, M., & Van Camp, G. (2009). [Genetics of otosclerosis.](#) *Otology & Neurotology*, 30(8), 1021–1032.

OBJECTIVES: Otosclerosis is a major cause of acquired hearing loss in adult life affecting exclusively the human temporal bone. Until recently, the etiopathogenesis of otosclerosis was still a matter of debate. Genetic research, however, has evolved enormously the last years and unveiled important clues regarding the cause of otosclerosis. The objective of this article is to review the genetics of otosclerosis with special attention for the links to the bone homeostasis of the otic capsule. **DATA SOURCES:** A detailed literature study was performed focusing on the recent genetic findings in otosclerosis and the special bone turnover of the otic capsule. A PubMed search and own research data were used to bring the relevant information for this review together. **CONCLUSION:** Unlike all other bones in the human skeleton, the otic capsule undergoes very little remodeling after development, possibly due to local inner ear factors. Otosclerosis is a process of pathologic increased bone turnover in the otic capsule, which in most cases leads to stapes fixation, resulting in a conductive hearing loss. Although environmental factors such as estrogens, fluoride, and viral infection have been implicated, it is clear that genetic factors play a significant role in the manifestation of otosclerosis. From a genetic viewpoint, otosclerosis is considered to be a complex disease with rare autosomal dominant forms caused by a single gene. Already, 7 monogenic loci have been published, but none of the genes involved have been identified. For the complex form of otosclerosis, caused by an interaction between genetic and environmental factors, the first susceptibility genes were identified by case-control association studies. All 3 replicated genes, TGFB1, BMP2, and BMP4, are a part of the transforming growth factor-beta1 pathway. Data from both genetic association studies and gene expression analysis of otosclerotic bone showed that the TGF-beta1 pathway is most likely an important factor in the pathogenesis of otosclerosis. [References: 153]

Hormone and gender differences in otosclerosis

Ricci, G., Gambacorta, V., Lapenna, R., Della Volpe, A., La Mantia, I., Ralli, M., & Di Stadio, A. (2022). [The effect of female hormone in otosclerosis. A comparative study and speculation about their effect on the ossicular chain based on the clinical results.](#) *European Archives of Oto-Rhino-Laryngology*, 279(10), 4831–4838.



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Bone resorption, which can occur after the menopause, has long been considered to be due to the decrease of estrogen and so estrogen and estrogen/progestin treatment in women has been employed with the aim of slowing down the process. Other important factors have recently been considered, including follicle-stimulating hormone. The hormonal control of bone metabolism has taken on a new dimension since the description, within the last decade, of a major osteoclast inhibiting control system. The receptor activator of nuclear factor-kappaB (NF-kappaB) ligand (RANKL) produced by osteoblastic lineage cells, must bind with its receptor RANK, located on osteoclasts, in order to allow the maturation and activation of osteoclasts. The potential continuous bone loss is controlled by the decoy receptor osteoprotegerin (OPG) which competitively binds to RANKL and hence blocks the interaction of RANKL-RANK. Estrogen contributes to bone protection since it decreases the response of osteoclasts to RANKL and induces osteoclast apoptosis. But estrogen, alone and especially in synergy with progesterone, is a potent stimulator of prolactin release. Prolactin affects calcium metabolism and hyperprolactinemia associated with pregnancy, lactation, antipsychotic drug treatment, or aging is reflected in decreased bone mineral density. Long-term estrogen treatment in guinea pig results in hyperprolactinemia and has been shown to lead to hearing loss as well as bone dysmorphology of the otic capsule. Recent data show that prolactin decreases OPG and increases RANKL. OPG has been shown to be expressed at high levels in the cochlea and OPG knock-out mice have indeed abnormal remodeling of the otic capsule and resorption of the auditory ossicles. So estrogen-induced hyperprolactinemia could oppose estrogen protection by the knock-down of the OPG bone protection system. This might explain why oral contraception treatment and hormone replacement therapies, involving estrogen together with progestin, increases the risk of otosclerosis and vestibular disorders. Hyperprolactinemia associated with pregnancy and lactation might also underlie the association of increased risk of otosclerosis with multiple pregnancies.

Clinical Evaluation/diagnosis/treatment

Silva, V. A. R., Pauna, H. F., Lavinsky, J., Guimarães, G. C., Abrahão, N. M., Massuda, E. T., ... & Castilho, A. M. (2023). [Brazilian Society of Otolaryngology task force-Otosclerosis: evaluation and treatment. *Brazilian Journal of Otorhinolaryngology*, 89, 101303.](#)

AB Objectives: To review and provide evidence-based recommendations for the diagnosis and treatment of otosclerosis.

Method(s): Task force members were educated on knowledge synthesis methods, including electronic database search, review and selection of relevant citations, and critical appraisal of selected studies. Articles written in English or Portuguese on otosclerosis were eligible for inclusion. The American College of Physicians' guideline grading system and the American Thyroid Association's guideline criteria were used for critical appraisal of evidence and recommendations for therapeutic interventions.

Result(s): The topics were divided into 2 parts: 1) Diagnosis - audiologic and radiologic; 2) Treatment - hearing AIDS, pharmacological therapy, stapes surgery, and implantable devices - bone-anchored devices, active middle ear implants, and Cochlear Implants (CI).

Conclusion(s): The pathophysiology of otosclerosis has not yet been fully elucidated, but environmental factors and unidentified genes are likely to play a significant role in it. Women with otosclerosis are not at increased risk of worsening clinical condition due to the use of contraceptives or during pregnancy. Drug treatment has shown little benefit. If the patient does not want to undergo stapedotomy, the use of hearing aids is well indicated. Implantable systems should be indicated only in rare cases, and the CI should be indicated in cases of profound deafness.





Foster, M. F., & Backous, D. D. (2018). Clinical evaluation of the patient with otosclerosis. *Otolaryngologic Clinics of North America*, 51(2), 319-326. For a copy of the full text please email library@somersetft.nhs.uk

Otosclerosis is a disorder presenting most commonly with unilateral conductive hearing loss. It can present as a mixed hearing loss also. Evaluation for otosclerosis relies on a specific history and physical examination, including tuning fork assessment and audiometric testing. Otosclerosis differs from other etiologies in that symptoms of imbalance are rare, and the ear most commonly appears normal on otoscopy.

Batson, L., & Rizzolo, D. (2017). Otosclerosis: An update on diagnosis and treatment. *Jaapa*, 30(2), 17-22. For a copy of the full text please email library@somersetft.nhs.uk

Otosclerosis is a complex and progressive disease of pathological bone remodeling that affects the otic capsule of the temporal bone, resulting in hearing loss. Although traditional diagnostic methods are still used, improvements in technology and research have paved the way for additional diagnostic techniques and advancements. The traditional treatment of otosclerosis, stapes surgery, is now being augmented or replaced by innovations in hearing aid technology and cochlear implants. Earlier diagnosis of otosclerosis can occur through understanding of the cause, risk factors, and current diagnostic testing.

Pathophysiology/Etiology

Rudic, M., Keogh, I., Wagner, R., Wilkinson, E., Kiros, N., Ferrary, E., ... & Zarkovic, N. (2015). The pathophysiology of otosclerosis: Review of current research. *Hearing research*, 330, 51-56. For a copy of the full text please email library@somersetft.nhs.uk

Otosclerosis is a complex disease of the human otic capsule with highest incidence in adult Caucasians. So far, many possible etiological factors like genetics, HLA, autoimmunity, viruses, inflammation, and hormones have been investigated but still the development of the disease remains unclear. Currently, the surgical replacement of stapes (stapedotomy) remains the best possible treatment option. In this review, we analyze different etiological factors studied so far in otosclerosis pathophysiology and discuss most recent findings and possible new research pathways.

Schrauwen, I., & Van Camp, G. (2010). The etiology of otosclerosis: a combination of genes and environment. *The Laryngoscope*, 120(6), 1195-1202. For a copy of the full text please email library@somersetft.nhs.uk

Otosclerosis is a common form of hearing loss characterized by abnormal bone remodeling in the otic capsule. It is a complex genetic disease, caused by a combination of genetic and environmental factors. During the past decade, several attempts have been made to identify factors for otosclerosis. This review provides an overview of the current understanding of the etiology of otosclerosis and describes the genetic and environmental factors that have been implicated in the disease. Environmental factors include fluoride and viral factors, particularly measles. Genetic association studies for otosclerosis have reported several associations of genetic variants that influence the risk of disease, mainly involving bone remodeling pathways, although their individual risk contributions are small. Rare monogenic forms of otosclerosis also exist, which are caused by a mutation in a single gene leading to a clear familial segregation of the disease. Linkage analysis of large otosclerosis families has led to the identification of seven loci, and recently evidence was found that T cell receptor beta is a gene responsible for familial otosclerosis, suggesting an underlying immunological pathway. However, this might also represent an autoimmune process, a hypothesis that is supported by other data as well. In conclusion, a variety of pathways have been identified to be involved in the development of





otosclerosis, showing that distinct mechanisms involving both genetic and environmental risk factors can influence and contribute to a similar disease outcome.

Karosi, T., Szekanecz, Z., & Sziklai, I. (2009). Otosclerosis: an autoimmune disease?. *Autoimmunity reviews*, 9(2), 95-101. For a copy of the full text please email library@somersetft.nhs.uk

Objectives: To review our current knowledge of the etiopathogenesis of otosclerotic bone remodeling including genetics, viral infection, autoimmunity and inflammation and to discuss disease pathogenesis with relevance for pharmacotherapy.

Systematic review methodology: Relevant publications on the etiopathogenesis, molecular biology, genetics and histopathology of otosclerosis from 1984 to 2009 were analyzed.

Results and conclusions: Otosclerosis is a bone remodeling disorder of the human otic capsule, however, the etiopathogenesis remains unclear. Genetic predisposition, disturbed bone metabolism, persistent measles virus infection, autoimmunity, hormonal and environmental factors also may play contributing roles in the pathogenesis of otosclerosis. Since, diagnosis of otosclerosis is still based on histopathological examination of the removed stapes footplate, systemic prospective studies based on comprehensive histopathological and molecular biological analysis are necessary to get further information about the background of disease.

Epidemiology

Niedermeyer, H. P., Häusler, R., Schwub, D., Neuner, N. T., Busch, R., & Arnold, W. (2007). [Evidence of increased average age of patients with otosclerosis](#). In *Otosclerosis and Stapes Surgery* (Vol. 65, pp. 17-24). Karger Publishers.

Otosclerosis is an inflammatory disease of the human temporal bone which was assumed to affect up to 10% of the Caucasians. Histologic otosclerosis has an incidence of 3.4%. It is considered as a major cause of hearing loss in Western countries while a low incidence is observed among Africans. Many hypotheses about its origin had been formulated in the past. Otosclerosis genes (OTSC1-5) and collagen 1 genes are mutated in some familial cases of otosclerosis. On this genetic background, a common environmental factor such as a measles virus infection might be the triggering factor. Studies in the past indicated a distribution of otosclerosis among men and women of 1:1.4. Our study was designed to analyze the age of patients with otosclerosis at the time of surgery in the eighties and the nineties of the last century. Patients suffering from clinical otosclerosis who underwent stapedectomy between 1978 and 1999 with complete clinical data available (n = 1,351) were included in the study. Age and gender distribution, the age difference between men and women and the influence of gender and the year of recruitment were evaluated. Statistical analyses demonstrated an increase in the average age of patients with clinical otosclerosis from the eighties to the nineties (p = 0.012). The gender distribution showed no statistically significant variation (p = 0.398). These data might reflect an improved health consciousness among the elder population or could be the result of increased health awareness in the seventies and eighties. Finally, in the early seventies, measles virus vaccination was introduced in Germany and the shift of age could be the result of the measles virus immunization campaign.

Neuner N.T., & Hausler, R. (2001). [Epidemiology of otosclerosis in the past 20 years](#). [Epidemiologie der otosklerose in den vergangenen 20 jahren.] *Oto-Rhino-Laryngologia Nova*, 11(4), 123-129.

Objective: This is a retrospective evaluation of a series of 916 patients with stapedectomy performed between 1978 and 1997 at the ENT Department of the University Hospital of Berne.



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	Pubmed		HMIC		BMJ Best Practice
X	Medline		Social Policy and Practice		Cochrane Library
	Emcare		CINAHL		TRIP
X	Embase		PsycINFO		Grey Literature
	AMED		UpToDate	X	Google Scholar LitMaps

PURPOSE OF SEARCH			
	Patient info/health & well being	X	Clinical decision making (inc. patient care)
	Executive Team support		Research/Education/Professional development
	Quality Improvement		Primary Care & Neighbourhoods Directorate support
	KM/Management decision making		Other

USER CATEGORY OF REQUESTOR			
	Medical students		Patients/public
	Nursing/midwifery students		Physician Associates
	Junior doctors		Public Health (Somerset CC)
	Nurses/Midwives	X	Consultant
	Allied Health professionals		





HAS PERMISSION TO SHARE THE RESULTS BEEN OBTAINED FROM THE REQUESTOR?

X	YES - share		NO – do not share
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KEY WORDS/SEARCH STRATEGY INCLUDING MESH HEADINGS	LIMITS USED
<ol style="list-style-type: none">1. otosclerosis.ti.2. Otosclerosis/3. or/1-24. (estrogen* or oestrogen* or oral contraceptive* or oral contraception or progestogen or Progesterone or Utrogestan or norgestrel or levonorgestrel or desogestrel or norgestimate or gestodene or Estradiol or Estrogen receptor or Estrone or Estriol or Folliculin or Estrogenic hormone* or Oestradiol or Oestrone or Oestriol).ti,ab.5. Estrogens/6. or/4-57. 3 and 6	

