Oral contraceptive pill use and abnormal menstrual cycles in women with severe condylar resorption: A case for low serum 17\(\beta\)-estradiol as a major factor in progressive condylar resorption

Michael J. Gunson,a G. William Arnett,a Bent Formby,b Charles Falzone,c Ruchi Mathur,d and Carolyn Alexanderd
Santa Barbara and Los Angeles, Calif

Introduction: Progressive condylar resorption has been described for many years. Because condylar resorption favors women over men, many have thought that a prominent systemic factor for the pathogenesis of this disease might be related to sex hormones.

Methods: Over a 3-year period, 27 women without autoimmune disease came to our office for orthognathic surgical correction of their skeletal deformity secondary to severe condylar resorption. They all showed radiographic evidence of severe condylar resorption. Sex hormone dysfunction was evaluated, and midcycle serum levels of 17\(\beta\)-estradiol were measured. Use of exogenous hormones was also documented. Results: Twenty-six of the 27 women with severe condylar resorption had either laboratory findings of low 17\(\beta\)-estradiol or a history of extremely irregular menstrual cycles. Of the 27 women, 25 showed abnormally low levels of serum 17\(\beta\)-estradiol at midcycle. Two subsets were identified in the group with low 17\(\beta\)-estradiol. The first did not produce estrogen naturally (8 of 27), and the second had low 17\(\beta\)-estradiol levels secondary to oral contraceptive pill (OCP) use (19 of 27). Of the 19 OCP users, all 19 reported that chin regression and open bite changes occurred after starting OCP use. Nine of the 19 reported these condylar resorption symptoms within the first 6 months of starting the OCP.

Conclusions: Whether induced by ethinyl estradiol birth control or by premature ovarian failure, low circulating 17\(\beta\)-estradiol makes it impossible for the natural reparative capacity of the condyle to take place in the face of local inflammatory factors. This leads to cortical and medullary condylar lysis. (Am J Orthod Dentofacial Orthop 2009;136:772-9)

Condylar resorption has been described for many years and by many authors. Aggressive condylar resorption is multi-factorial. Three groups of factors have been reported as contributors to condylar resorption as described by Arnett et al in 1996 (Fig 1): (1) bite treatment, which produces condylar position changes with compression, has been shown to generate remodeling; (2) local factors, which produce compression such as internal derangement (ID) and clenching, produce varying degrees of remodeling; and (3) systemic factors such as systemic arthridities and hyperparathyroidism have also been known to cause or exacerbate condylar resorption.

Because condylar resorption favors women over men, many have thought that a prominent systemic factor for the pathogenesis of this disease might be related to sex hormones.

To clinically evaluate the influence of sex hormones on condylar resorption, we reviewed the endocrine function of women who came to our office in Santa Barbara, Calif, from 2005 through 2008 with severe condylar resorption.

MATERIAL AND METHODS

Over a 3-year period, 27 women with no history of autoimmune disease came for orthognathic surgical correction of their skeletal deformity secondary to severe condylar resorption. They were selected for this study solely on imaging evidence of severe condylar resorption either currently active or active in the past. The average age at the time of condylar resorption was 26 years (range, 15-45 years). Condylar resorption was diagnosed by history, physical examination, and radiographic examination. All subjects
gave a history of spontaneous regressive change in their dental occlusion and development of a more retrusive chin position. The timing of these changes was carefully noted from the patient’s history, the parent’s history, and the clinician’s notes and comments. The clinical examination of these patients showed a Class II dental and skeletal relationship with anterior open bite (Figs 2 and 3). Lateral cephalometrics showed a steep mandibular occlusal plane (SD, >3), anterior open bite (SD, >2), and pogonion retrusion (SD, >2) (Table I; Figs 4 and 5). Cone-beam computed tomography scans showed condyles with flat surfaces, decreased head bulge, pseudocystic lesions, and cortical erosions (Fig 6).

An in-depth medical history of each patient was used to evaluate sex hormone dysfunction. Information on each woman’s growth and development (full-term births, breast development, and hair distribution), onset of menses (menarche), disruption of menstrual cycle (months of amenorrhea, midcycle spotting, and fluctuating cycle length), painful menses, need for hormone replacement, use of hormonal birth control, and abnormal Pap smear information were obtained. Any exogenous hormone usage was documented for purpose, time, and duration.

Samples of 17β-estradiol were analyzed by using liquid chromatography-tandem mass spectrometry at several laboratories. Venous blood samples of serum 17β-estradiol were drawn at midcycle (days 14-16).
and compared with known midcycle norms. All subjects were serum negative for markers of systemic arthritides, cyclic citrullinated peptide, antinuclear antibodies, and rheumatoid factor.

RESULTS

Of the 27 women with severe condylar resorption, 26 had either laboratory findings of low 17β-estradiol or a history of extremely irregular menstrual cycles (amenorrhea or cycle length changes). Sixteen of the 27 had both low 17β-estradiol and irregular periods (Table II). Of the 27 women, 25 showed abnormally low levels of serum 17β-estradiol at midcycle, and the other 2 were at the low end of normal (Table II). The normal level of 17β-estradiol at midcycle is more than 200 pg per milliliter. In the women with low 17β-estradiol, 2 subsets were identified. The first group did not produce estrogen naturally (8 of 27), a process called early ovarian failure. The second group had low 17β-estradiol levels secondary to ethinyl estradiol (EE) and progestin oral contraceptive use (19 of 27). Of the 19 oral contraceptive pill (OCP) users, all 19 reported that chin regression and open-bite changes occurred after starting OCP use. Nine of the 19 reported condylar resorption symptoms within the first 6 months of starting the OCP.

Of the 27 women with severe condylar resorption, 17 had a history of irregular menstrual cycles. Seven of the 17 with irregular menstrual cycles had episodes of frank amenorrhea (no cycle), which corresponded temporally with their symptoms of condylar resorption.

DISCUSSION

The least understood and investigated aspect of aggressive condylar resorption is the possible contribution of systemic factors. Often and prominently, ID has been assigned almost full responsibility for condylar resorption, in spite of many studies showing various changes associated with ID.18-25 It has been demonstrated that ID in 1 patient causes minimal morphologic changes, whereas another patient might have severe condylar changes with the same level of ID severity. Our findings suggest that previously undiagnosed hypoestrogenemia might explain the exaggerated condylar resorption elicited by common joint compressive factors such as

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<th>ICR patients</th>
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Overbite, overjet, and MdOP for 27 patients. The mean overbite measured from the tip of the upper incisor to the tip of the lower incisor was −1 mm (normal +2 to +3). The mean overjet also measured from tip to tip was 7 mm (normal +3). The MdOP mean was very steep at 106° (normal range 92 to 95°).

ICR, Idiopathic condylar resorption; MdOP, mandibular occlusal plane.
ID, bruxism and, condyle displacement with bite treatments (Fig 1).

In 1993, Abubaker et al\textsuperscript{14} reported that women with joint symptoms were 5 times more likely to have intracapsular estrogen receptors than women without temporomandibular joint (TMJ) symptoms. It is possible that those findings were a manifestation of low circulating estradiol that led to upregulation of estrogen receptors on the articular tissues.

In regard to condylar resorption, however, more pertinent pathways related to low 17$\beta$-estradiol are likely intercellular communication pathways (cytokines). The recent explosion of osteoporosis and arthritis research has helped uncover the balancing act between 2 cytokines—receptor activator for nuclear factor $\kappa$ B ligand (RANKL), osteoprotegerin (OPG)—and 17$\beta$-estradiol. The balance between these 2 cytokines has much to do with maintaining bone integrity. These cytokines are produced by osteoblasts, T-cells, and synoviocytes in response to other hormones or cytokines and direct stress on the cells. RANKL has been shown to promote bone resorption via osteoclastogenesis and osteoclastic activity.\textsuperscript{26} OPG, on the other hand, interferes with RANKL and blocks its action, thus preserving local bone. When the RANKL/OPG ratio is elevated (more RANKL than OPG), osteoclastic activity is suppressed, and osteoblastic activity predominates.\textsuperscript{26,27} The imbalance of RANKL/OPG in the TMJs of symptomatic patients has been shown.\textsuperscript{21,28-30}

How does 17$\beta$-estradiol affect the OPG/RANKL balance? 17$\beta$-estradiol has been shown to be a potentialator of OPG release, thus protecting bone in the face of local and systemic inflammatory factors.\textsuperscript{31} Conversely, when 17$\beta$-estradiol is deficient, OPG is not promoted, allowing local and systemic inflammatory factors to inhibit new bone formation or promote resorption of bone mass.\textsuperscript{31-33} Liang et al\textsuperscript{34} showed OPG up-regulation in human periodontal cells when exposed to 17$\beta$-estradiol. This same reaction was also shown in explanted human TMJ cells.\textsuperscript{30}

In addition to the OPG/RANKL effect, women with consistently low circulating 17$\beta$-estradiol levels have

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
ICR patients & Irregular menses & EE for OCP & OCP name & Midcycle estradiol \\
\hline
1 & Y$^\dagger$ & N & * & 143.00$^\dagger$ \\
2 & N & Y$^\dagger$ & Kariva & Undetectable$^\dagger$ \\
3 & Y$^\dagger$ & Y$^\dagger$ & Desogen & 84.00$^\dagger$ \\
4 & N & N & * & 71.00$^\dagger$ \\
5 & N & Y$^\dagger$ & Yasmin & 209.00$^*$ \\
6 & Y$^\dagger$ & Y$^\dagger$ & Yaz & 47.00$^\dagger$ \\
7 & Y$^\dagger$ & N & * & 37.00$^\dagger$ \\
8 & Y$^\dagger$ & Y$^\dagger$ & Seasonale & Undetectable$^\dagger$ \\
9 & Y$^\dagger$ & Y$^\dagger$ & Yasmin & 128.00$^\dagger$ \\
10 & Y$^\dagger$ & N & * & 46.00$^\dagger$ \\
11 & Y$^\dagger$ & Y$^\dagger$ & Yaz & Undetectable$^\dagger$ \\
12 & Y$^\dagger$ & Y$^\dagger$ & Seasonale & 228.00$^*$ \\
13 & Y$^\dagger$ & N & * & 4.00$^\dagger$ \\
14 & N & Y$^\dagger$ & Orthotricyclin Lo & 49.00$^\dagger$ \\
15 & N & Y$^\dagger$ & Orthotricyclin & 31.00$^\dagger$ \\
16 & Y$^\dagger$ & N & * & 65.00$^\dagger$ \\
17 & Y$^\dagger$ & Y$^\dagger$ & Allesse & 120.00$^\dagger$ \\
18 & Y$^\dagger$ & N & * & 95.00$^\dagger$ \\
19 & N & N & * & 40.99$^\dagger$ \\
20 & N & Y$^\dagger$ & LoEstrin & 121.00$^\dagger$ \\
21 & N & Y$^\dagger$ & Orthotricyclin & 17.00$^\dagger$ \\
22 & Y$^\dagger$ & Y$^\dagger$ & Sprintec & 65.00$^\dagger$ \\
23 & Y$^\dagger$ & Y$^\dagger$ & Lo-Ovral & 13.00$^\dagger$ \\
24 & Y$^\dagger$ & Y$^\dagger$ & Orthotricycline & 92.10$^\dagger$ \\
25 & Y$^\dagger$ & Y$^\dagger$ & Seasonale & 22.00$^\dagger$ \\
26 & N & Y$^\dagger$ & Yasmin & Undetectable$^\dagger$ \\
27 & N & Y$^\dagger$ & Yaz & 83.00$^\dagger$ \\
\hline
Mean & & & & 49.58 \\
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\end{tabular}
\caption{Findings of patients with severe condylar resorption}
\end{table}

Occurrence of irregular menses, ethinyl estradiol oral contraceptive pill use (OCP), brand name of OCP, and midcycle 17$\beta$-estradiol results are shown. Note only 2 of the 27 patients had normal levels of 17$\beta$-estradiol at midcycle and one of them had already stopped their OCP prior to the lab draw.

ICR, Idiopathic condylar resorption; Y, yes; N, no.

*Estradiol level after stopping OCP use; $^\dagger$positive finding.
increased inflammatory cytokines and resultant increases in arthritic symptoms and decreases in bone mineral density.\textsuperscript{35-40}

It has been shown that matrix metalloproteinase (MMP) elevation has been identified in patients with aggressive condylar resorption.\textsuperscript{41-43} When present in joint

Fig 5. Five time periods, frontal and sagittal tomographic representation of severe progressive condylar resorption. Each column represents the same time point. Column 1 is presurgical. The left joint is small with preexisting condylar changes, and the right joint has an irregular cortical outline in the sagittal view. Column 2 is 12 days postsurgery. The joint spaces in all views have decreased for both sides, and the right joint has been sagitally posteriorized (compressed). Column 3 is 4 months postsurgery. Note the further decrease in joint spaces. Column 4 is 6 months postsurgery. Note the osteolytic lesions in all views. Column 5 is 12 months postsurgery. Note condylysis in all views.
It is likely that some local stress factors that were not considered in this study—e.g., malocclusion, dental splints, orthodontics, disc displacement, orthognathic surgery—had an influence on condylar change. The fact that most of our female patients with severe condylar resorption had signs and symptoms of 17β-estradiol deficiency, however, makes a strong case for 17β-estradiol deficiency as an aggressive systemic factor in severe resorption. Whether induced by EE birth control or through premature ovarian failure, low circulating 17β-estradiol appears to make it impossible for the natural reparative capacity of the bony condyle to take place in the face of local inflammatory factors (Fig 6). This then leads to cortical and medullary condylar lysis.

We recommend that, until further studies are performed, clinicians should be careful with female patients with the above-described signs and symptoms of 17β-estradiol deficiency. A review of the patient’s gynecologic and endocrine histories is warranted. If there seems to be an association between OCP use and condylar resorption in a patient, recommending cessation of the OCP to the patient’s physician might be beneficial. Minimizing treatments that increase condylar loading in the face of 17β-estradiol deficiency can also be helpful.

Obviously, to further elucidate the relationship of 17β-estradiol and condylar resorption, prospective and controlled studies are needed.

**REFERENCES**


