# Ovariectomy

Ovariectomy causes an expansion of the T-cell pool in the BM, spleen, and lymph nodes by increasing T-cell activation, a phenomenon that results in increased T-cell proliferation and life span.

From: Bone Disease of Organ Transplantation, 2005

Related terms:

Hysterectomy, Neoplasm, Estradiol, Ovary, Estrogen, Breast Cancer, Menopause, Testosterone, Progesterone

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## Castration and Cryptorchid Surgery

Neal Ashton, in Veterinary Reproduction and Obstetrics (Tenth Edition), 2019

### Indications

Routine ovariectomy of the mare is indicated to reduce unwanted 'mare-like' behaviour and prevent oestrus. It is likely that prevention of inappropriate aggressive and dominant behaviour is most effective if ovariectomy is carried out in young mares soon after the behaviour becomes apparent. However, the effects of ovariectomy on mare behaviour have not yet been fully investigated. Prepubertal ovariectomy of mares to prevent inappropriate behaviour is not currently undertaken, and its effectiveness has not been investigated. Ovariectomy is also indicated in cases of ovarian pathology, most commonly a granulosa cell tumour in which the mare may demonstrate a broad range of clinical signs, and there is commonly substantial enlargement of the ovary.



## Premenopausal Reproductive and Hormonal Characteristics and the Risk for Osteoporosis

MARYFRAN SOWERS, in Osteoporosis (Third Edition), 2008

### X. OOPHORECTOMY

Oophorectomy is commonly cited as an example of hypoestrogenism with an impact on measures of calcium metabolism [242], fracture [94], and bone mineral content in both White [243–246] and Japanese women [247, 248]. Richelson *et al.* [243] compared BMD of the radius, femoral neck, and lumbar spine in women in their fifth decade who had undergone oophorectomy 20 years earlier, with BMD measured at the same sites of women in their seventh decade who had undergone spontaneous menopause, also some 20 years earlier. BMD of the two groups of women were almost the same and suggested that estrogen is a factor as important as aging in determining the level of bone density. Indeed, Aitken *et al.* [244] reported that bone density, as measured by standard aluminum equivalents, was lowest in women who had undergone oophorectomy at earlier ages.

#### A. Studies of the Effect of Oophorectomy on Bone

Several studies have attempted to define the nature of the rate of bone loss following oophorectomy. Cross-sectional data of Stepan *et al.* [249] suggested a mean loss of 2.8% of the metacarpal cortical area and 8% of the lumbar spine (by dual photon

densitometry) in the first year following oophorectomy. Using statistical modeling of secondary data of the cortical area, Reeve [250] projected that there was a doubling of bone resorption following oophorectomy. Genant *et al.* [251] estimated that annual bone mineral losses were approximately 8% in the vertebral spongiosum and about 2% in the peripheral cortex when evaluated by quantitative computed tomography. In contrast, Hreshchyshyn *et al.* [252] did not observe a more pronounced rate of change in women after oophorectomy as compared to naturally menopausal women. There was a modest increase in fracture risk (standardized morbidity ratio 1.4, 95% CI, 1.0–2.0) among women in Rochester, Minnesota, who underwent bilateral oophorectomy between 1950 and 1979 [253].

Bone turnover markers reflect higher bone resorption relative to bone formation in the period following oophorectomy [247, 249]. Investigators observed an increase in serum osteocalcin concentrations beginning 1–2 months following oophorectomy and increasing up to 1 year of follow-up. Bone-specific alkaline phosphatase also rose, although at a slower rate than osteocalcin levels [249].

Ohta *et al.* [247, 248] proposed that the bone loss in women after oophorectomy encompasses more than the diminution of estradiol. Oophorectomy also includes a marked reduction of estrone and androstenedione concentrations to values that are significantly lower than those concentrations measured in menopausal women. Ohta *et al.* [247] indicated that postmenopausal women retain some estrone secretion from ovarian interstitial cells that may not be present in women with oophorectomy.

A number of studies have reported that the calciotropic hormones, particularly PTH, do not undergo significant changes following oophorectomy [247, 249, 252], suggesting that the bone loss of oophorectomy is not dependent on the homeostatic regulation of serum calcium. Yet to be evaluated is the relationship to PTH, using a contemporary assay for intact PTH.

While oophorectomy provides one model for the evaluation of ovarian hormone deprivation and BMD, that relationship may be confounded by those events that gave rise to the context for the oophorectomy. Oophorectomy with hysterectomy is performed for the treatment of malignancy, pelvic inflammatory disease, endometriosis, uterine fibroids, and other conditions that may influence BMD independently of the surgical procedure and its hormonal sequelae.

Estrogen replacement is a frequently proposed strategy following oophorectomy, although data describing the frequency of its prescription, compliance, and duration of use appear to be unavailable for the general population. Aitken *et al.* [244] estimated that women lost approximately 8% of metacarpal bone mass in the first 2 years following oophorectomy in comparison to no measurable loss in women treated with mestranol (10–20 mcg/day). The same study also allotted a group of women to mestranol treatment who were 3 and 6 years postoophorectomy. While the women who were 3 years postoophorectomy maintained bone density, those women who were 6 years postsurgery continued to lose bone and manifested no responsiveness to the mestranol. The investigators interpreted this to mean that there is a limited window of time following oophorectomy when bone is most responsive to hormone replacement.

A number of treatments for the bone loss associated with oophorectomy, apart from hormone replacement [254], have been evaluated. In a clinical trial of a synthetic flavonoid, Gambacciani *et al.* [255] demonstrated that women with oophorectomy/hysterectomy (n = 16) acting as controls had significant loss of radial bone mass and elevated hydroxyproline levels in comparison to women in the treated group (n = 16) 1 year following surgery. The prophylactic administration of salmon calcitonin in oophorectomized women apparently inhibited skeletal resorption as measured by radial bone mineral content and the behavior of Gla protein (osteocalcin) and hydroxyproline concentrations [256].



# Bone and the Immune System

M. Neale Weitzmann PhD, Roberto Pacifici MD, in Bone Disease of Organ Transplantation, 2005

## V MECHANISMS OF ESTROGEN REGULATION OF T-CELL PRODUCTION OF TNF

Ovariectomy up-regulates T-cell TNF production by increasing the number of TNF-producing T cells without altering the amount of TNF produced by each T cell [16]. This is the result of a complex pathway, summarized in Figure 3. Ovariectomy causes an expansion of the T-cell pool in the BM, spleen, and lymph nodes by increasing T-cell activation, a phenomenon that results in increased T-cell proliferation and life span. Ovariectomy increases T-cell activation by enhancing antigen presentation by BMM; this is a result of the ability of estrogen deficiency to up-regulate the expression of major histocompatibility complex II (MHCII)

this is a result of the ability of estrogen deficiency to up-regulate the expression of major histocompatibility complex II (MHCII). Although the mechanism of T-cell activation elicited by estrogen deficiency is similar to that triggered by infections, the intensity of the events that follow estrogen withdrawal is significantly less severe. This process should be envisioned as a partial increase in T-cell autoreactivity to self-peptides, resulting in a doubling of the pool of effector $CD4^+$ cells. Modulation of antigen presentation by estrogen is BMM- and dendritic cell-specific because no changes are induced by ovariectomy in B cells and dendritic cells, the other two populations of professional antigen-presenting cells (APCs) [15].

The relevance of this mechanism *in vivo* was established by using DO11.10 mice, a strain in which all T cells recognize a single peptide epitope of chicken albumin (ovalbumin), which is not expressed in mice. In the absence of ovalbumin, APC of DO11.10 mice are unable to induces T-cell activation. If APC are a relevant target of estrogen, therefore, these mice should be protected from the increased T-cell proliferation, the suppression of activation-induced T-cell death, and the bone loss that follows ovariectomy. As predicted, ovariectomy fails to increase T-cell proliferation and lifespan in DO11.10 mice. As a result, ovariectomy fails to increase the pool of T cells and to induce bone loss in these mice [15]. In addition, injection of ovalbumin, which permits the generation of the appropriate MHC-peptide antigen for these T cells, restores the capacity of ovariectomy to expand the T-cell pool by targeting proliferation and apoptosis and inducing bone loss. These data demonstrate that antigen presentation, specifically the generation of appropriate peptide–MHC complexes, is critical to the process by which ovariectomy increases T-cell proliferation and lifespan and leads to bone loss. Furthermore, the finding that T cells from ovariectomized mice exhibit an increased response to ovalbumin (an antigen not present in mammals) demonstrates that ovariectomy increases the reactivity of APC to endogenous antigens, rather than stimulating the production of a new antigen or modulating antigen levels.

The mechanism just described hinges on the ability of APCs to present antigenic peptides bound to MHCII molecules to T cells. The question thus arises about the source of the involved antigens. Estrogen deficiency is likely to increase the reactivity of T cells to a pool of self and foreign antigens physiologically present in healthy animals. This is consistent with the fact that clones of T cells expressing T-cell receptor (TCR) directed against self antigens not expressed in the thymus survive negative selection during T-cell maturation [56, 57, 58, 59]. Such clones are known as autoreactive or self-reactive T cells and reside in peripheral lymphatic organs of adult individuals [60]. In addition, foreign antigens of bacterial origin are physiologically absorbed in the gut. As these peptides come in contact with immune cells locally and systemically they induce a low-grade T-cell activation [60]. Thus, a moderate immune response is constantly in place in healthy humans and rodents due to presentation by MHCII and MHCI molecules of both self and foreign peptides to $CD4^+$ and $CD8^+$T cells [61]. This autoreactive response is thought to be essential for immune-cell survival and renewal [62]. In summary, according to our hypothesis, ovariectomy would increase T-cell autoreactivity by up-regulating antigen presentation by BMM.

The effects of ovariectomy on antigen presentation and the resulting changes in T-cell activation, proliferation, and lifespan are explained by a stimulatory effect of ovariectomy on the expression of the gene encoding Class II Transactivator (CIITA). The product of the CIITA gene is a non-DNA binding factor that functions as a transcriptional coactivator when recruited to the MHCII promoter by interaction with promoter-bound factors [63, 64]. CIITA expression is, indeed, required and sufficient for the stimulation of antigen presentation in BMM.

CIITA expression is regulated by four distinct promoters that direct the transcription of four separate first exons spliced to a common second exon [65]. While initial studies revealed that IFNγ-inducible expression in murine BMM is regulated exclusively by promoter IV [65, 66], it is now recognized that both promoter I and IV account for IFNγ-induced CIITA in BMM *in vitro* and *in vivo* [67, 68].

CIITA is constitutively expressed in B cells and dendritic cells, but not in BMM. The physiologic inducer of CIITA in BMM is IFNγ. Increased CIITA expression in BMM from ovariectomized mice is a result of the ability of ovariectomy to increase both the T-cell production of IFNγ and the responsiveness of the CIITA gene to IFNγ in BMM [15]. This second regulatory mechanism is revealed by the greater expression of CIITA and MHCII by BMM from ovariectomized mice as compared to BMM harvested from estrogen-replete animals, in response to an equal stimulation with IFNγ [15].

That ovariectomy increases T-cell production of IFNγ was demonstrated both by measuring the level of the cytokine in the culture media of purified T cells cultured for 24 hours and by FACS analysis of unfractionated BM. IFNγ production by T cells is induced by either a cyclosporin-A-sensitive T cell receptor (TCR)–dependent mechanism, mediated by T-cell activation or by the cytokines IL-12 and IL-18 through activation of the MAP kinase p38. The increased production of IFNγ by T cells from ovariectomized mice is suppressed by *in vitro* treatment with the selective p38 inhibitor SB203580, but not by the activation inhibitor cyclosporin-A, indicating that increased IFNγ production by $CD4^+$ cells in ovariectomized mice is cytokine-driven. The expression of the IL-12 and IL-18 genes in BMM is induced by NFκB and AP-1, nuclear proteins whose transcriptional activity is directly repressed by estrogen [69, 70, 71]. Unstimulated BMM such as those from estrogen-replete mice are known to express low or undetectable levels of NFκB and AP-1 [72]. Accordingly, ELISAs revealed that sham BMM express minimal levels of IL-12 and IL-18, and ovariectomy potently increases secretion of IL-12 and IL-18 while *in vitro* treatment with 17β estradiol represses it. Thus, one mechanism by which estrogen represses CIITA is by decreasing IFNγ production via an inhibitory effect on the BMM production

of IL-12 and IL-18.

It should also be noted that because CIITA expression in T cells stimulates IFNγ production [73], and IFNγ stimulates both its own inducers, IL-18 and IL-12, and IL-12 receptor expression [74, 75], ovariectomy triggers an amplification loop leading to a further increase in the level of IFNγ and the resulting induction of CIITA.

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# Breast Cancer

Richard J. Santen, in Yen & Jaffe's Reproductive Endocrinology (Sixth Edition), 2009

## Surgical Oophorectomy.

Prophylactic oophorectomy represented the first adjuvant endocrine therapy for breast cancer. Although initially thought to be ineffective, recent meta-analyses demonstrate clear benefit with a 6% absolute survival advantage at 15 years for patients younger than 50 years of age who are lymph node negative and a 12.5% survival advantage for node-positive patients (Fig. 27-22). Because receptor status was unknown in patients in these trials, a large fraction of receptor-negative patients was likely included. Accordingly, one would have expected even better results if hormone receptor–positive patients only were so treated. In the advanced disease setting, surgical oophorectomy induces clinical benefit in approximately 50% of ER+ or PR+ patients.[98]

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# Premenopausal Reproductive and Hormonal Characteristics and the Risk for Osteoporosis

John F. RandolphJr., MaryFran R. Sowers, in Osteoporosis (Fourth Edition), 2013

## Oophorectomy

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# Androgens

Mona Al Mukaddam, Peter J. Snyder, in Osteoporosis (Fourth Edition), 2013

## Effect of Testosterone on Bone in Women Who Have Undergone Ovariectomy

Bilateral ovariectomy eliminates ovarian secretion of testosterone, so it is not surprising that postmenopausal women who have undergone bilateral ovariectomy have lower serum testosterone concentrations than age-matched women who have not. In one study, 11 women aged 55–64 years who had had bilateral ovariectomy had a mean serum testosterone concentration of 0.38nmol/L, compared to 0.66nmol/L in 74 women of the same age who had intact ovaries [46]. A similar difference was noted between ovariectomized and intact women 65–75 years. In another study, 123 ovariectomized women of mean age 73 years had a mean serum testosterone concentration of 0.29nmol/L and 438 intact women of mean age 74 years had a mean serum testosterone concentration of 0.56nmol/L [47].

When women in the same population who had had bilateral total ovariectomy and were treated with 1.25mg of esterified estrogens plus 1.25mg of methyltestosterone a day for 2 years, their spine BMD did increase more than in those who received 1.25mg of conjugated equine estrogen alone, but those who received 0.625mg of esterified estrogens a day plus 0.625mg of methyltestosterone did not experience a greater change in BMD than those who received 0.625mg of conjugated equine

estrogens alone [48]. In short, only those who took the higher dose of methyltestosterone experienced improvement in BMD, and whether that dose of testosterone is a physiologic replacement dose, or greater, is not known.

Another indicator of the consequences of testosterone deficiency in postmenopausal women who have been ovariectomized is their incidence of fractures compared to those who have not. Among 6295 women participating the Study of Osteoporotic Fractures, the incidence of fractures was no greater in the 583 women who underwent postmenopausal ovariectomy than in the 5712 women who did not [49].



# Therapeutic Areas I: Central Nervous System, Pain, Metabolic Syndrome, Urology, Gastrointestinal and Cardiovascular

C.R. Dunstan, ... M.J. Seibel, in Comprehensive Medicinal Chemistry II, 2007

## 6.21.4.1.1 Rat acute oophorectomy model of menopausal bone loss

Oophorectomy in rats results in development of a high turnover osteopenia, with most bone loss occurring over 4–6 weeks.[48] Treatment with estradiol is effective in inhibiting the bone loss. Thus, the rat has been found to provide a very useful model of the acute bone loss occurring in women following natural or surgical menopause due to estrogen withdrawal. Acute bone loss occurs in both young growing rats and mature rats following oophorectomy; however, it is preferable to use rats of at least 12 weeks of age that have a much reduced growth rate so that the results are not significantly influenced by growth-related effects of treatments. This model is particularly valuable in assessing treatments targeting bone resorption as inhibition of bone resorption effectively preserves normal bone mass. In contrast, oophorectomized mice are not a good model, as bone loss is variable and estradiol treatment is strongly anabolic, producing a profound osteosclerosis at high doses and indicating that hormonal regulation of bone mass is fundamentally different from that in rats and humans.



# Gynecologic and perinatal pathology

In Manual of Surgical Pathology (Second Edition), 2006

## Pathologic diagnostic/prognostic features sign-out checklist for ovarian carcinomas

### Specimen type*

Oophorectomy (right or left), salpingo-oophorectomy (right or left), subtotal oophorectomy (right or left), removal of tumor in fragments, hysterectomy with salpingo-oophorectomy, omentectomy.

### Tumor site*

Ovary (right or left), parenchymal growth, growth on surface, uninvolved.

### Specimen integrity*

Intact, ruptured, fragmented. List separately for right and left ovary.

### Tumor size*

Greatest dimension (additional dimensions optional).

### Histologic type*

Serous carcinoma, mucinous carcinoma, endometrioid carcinoma, clear cell carcinomas, transitional carcinoma, squamous carcinoma, undifferentiated carcinomas, borderline carcinomas, granulosa cell tumor, germ cell tumor. The WHO classification is recommended.

### Histologic grade*

Well, moderately, poorly differentiated.

***Endometrioid:***

Use grading system for endometrial carcinomas (see Box 22-2).

***Serous, clear cell, transitional, squamous:***

Use nuclear grading system (see Box 22-2).

***Immature teratoma*:**

See Table 22-7.

### Involvement of other organs/tissues

One ovary, both ovaries, omentum, uterus, fallopian tube, serosa of uterus, peritoneum, etc.

### Extent of invasion*

Tumor limited to ovaries, involvement of capsule, presence or absence on ovarian surface, presence or absence in ascites or peritoneal washings, extension and/or implants on uterus and/or tubes, microscopic or macroscopic peritoneal metastases.

Superficial tumors (<0.5 cm invasion into ovary) may be primary peritoneal carcinomas or metastases. Tumors at the hilum are more commonly metastatic carcinomas.

### Ovarian capsule

Intact or ruptured, relationship of rupture to carcinoma (i.e., is the malignancy at the site of the rupture).

### Regional lymph nodes*

Absent (N0), present (N1). Number of nodes examined, number with metastases.

### Distant metastasis*

Absent (M0), present (M1). Specify site, if known.

***Implants (for borderline tumors)****

***Non-invasive (epithelial) implants:*** Not present, present, site.

***Non-invasive (desmoplastic) implants:*** Not present, present, site.

***Invasive implants:***

Not present, present, site.

Size of peritoneal metastases (<2 cm or >2 cm).

### Venous/lymphatic (large/small vessel) invasion

Absent, present, indeterminate. This finding has not been clearly linked to prognosis. It is more commonly seen in tumors metastatic to the ovary.

### Cytology

Ascitic fluid or peritoneal washings: Positive or negative for malignant cells

### Other findings

Endometriosis (ovarian or extraovarian), endosalpingiosis, ovarian or tubal cysts, etc.

This checklist incorporates information from the ADASP (see www.panix.com/~adasp) and the CAP Cancer Committee protocols for reporting on cancer specimens (see www.cap.org/). The asterisked elements are considered to be scientifically validated or regularly used data elements that must be present in reports of cancer-directed surgical resection specimens from ACS CoC-approved cancer programs. The specific details of reporting the elements may vary among institutions.

The AJCC classification is presented in Table 22-8.

# Hormone Responsive Cancers

Richard J. Santen, ... Stephen H. Culp, in Yen & Jaffe's Reproductive Endocrinology (Seventh Edition), 2014

## Surgical Oophorectomy

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