Nonneoplastic Disorders of the Ovary

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Abstract

Histopathologists frequently receive oophorectomy specimens for a variety of reasons other than assessment of an ovarian neoplasm. Recognition of various incidental findings and nonneoplastic lesions in the ovary is therefore an important part of daily practice for histopathologists. Functional cysts can arise from follicular structures and lead to clinical symptoms, while stromal lesions can be associated with hormonal disturbances and secondary endometrial pathology. Ovarian inflammation can occur as part of pelvic inflammatory disease, in various viral and parasitic infections, as well as in noninfectious inflammatory conditions. Endometriosis is commonly encountered in the ovary, with variable features including formation of large endometriotic cysts. It is important to be aware and recognize a range of ovarian lesions that occur specifically in pregnancy to avoid unnecessary treatment. Ovarian torsion is a not uncommon gynecological emergency, and various miscellaneous lesions are frequently encountered during routine histopathological examination of the ovary. This chapter provides a summary of the main nonneoplastic conditions of the ovary that are likely to be encountered by histopathologists.

Introduction

The ovaries are received for histopathological examination for many reasons apart from their removal for assessment of an ovarian neoplasm. Oophorectomy is performed as part of staging for a range of other gynecological malignancies. Bilateral salpingo-oophorectomy may be performed in both premenopausal and postmenopausal women at the time of hysterectomy for benign conditions, and normal physiological findings and incidental pathological lesions can be detected. Women with a family history of ovarian cancer may undergo prophylactic bilateral salpingo-oophorectomy as prophylaxis. Hence, understanding of normal ovarian histology and nonneoplastic ovarian histopathology is

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essential for both general and specialist gynecological histopathologists on a daily basis. This chapter considers the main nonneoplastic conditions encountered in histopathological examination of the ovary.

Follicular and Stromal Lesions

Cystic Follicles and Follicular Cysts

Cystic Follicles

Follicular development occurs throughout reproductive life and, since follicle development does not occur within a single cycle, the various stages of follicle development can be observed in the ovaries from women of reproductive age. Cystic follicles are within the range of normal follicular development. They arise in reproductive age women when Graafian follicles do not rupture to release the ovum and eventually undergo resorption. Cystic follicles can be solitary or multiple and macroscopically appear as smooth-walled cortical cysts, usually <1 cm diameter, that contain watery fluid. By definition once cystic follicles reach 3 cm diameter, they are termed follicle cysts. Cystic follicles are usually lined by inner granulosa cells and outer theca cells which show varying luteinization. Some may resemble corpora lutea and are lined by luteinized granulosa cells and theca cells.

Follicle Cysts

Etiology and Pathogenesis: Follicle cysts usually present in nonpregnant women of reproductive age, particularly around menarche and in the perimenopause, but rarely can occur in newborns and childhood [1] and in postmenopausal women [2]. The etiology is likely to reflect disordered function of the pituitary-ovarian axis. Non-luteinized follicle cysts secrete estrogen and arise by excessive ovarian stimulation, either by endogenous FSH or exogenous ovulation-inducing agents. Granulosa lutein cysts secrete progesterone and may arise from failure of follicular rupture at ovulation. Theca-lutein cysts show luteinization of the theca interna and secrete androgens; they develop with prolonged exposure to LH or βhCG such as in polycystic ovarian syndrome, pregnancy, or ovarian hyperstimulation syndrome.

Clinical Features: Cystic follicles are usually asymptomatic but may present with mild vague pelvic pain. Non-luteinized follicle cysts are also often an incidental finding but sometimes present with menstrual irregularities due to estrogen production. Granulosa lutein cysts secrete progesterone but rarely at sufficient levels to disrupt the menstrual cycle [3]. Occasionally, follicle cysts may rupture and cause acute abdominal pain and hemoperitoneum [4] or present as an ovarian mass. Ultrasound is usually reassuring. Cyst aspiration with cytological assessment and measurement of estradiol has been reported as a diagnostic approach [5, 6], but initial treatment is usually by observation rather than aspiration due to the theoretical potential of dissemination of malignant cells. A randomized controlled trial of cyst aspiration compared with observation in 269 women aged 14–81 years reported no difference in the resolution rate at 6 months of ultrasound-detected simple ovarian cysts after cyst aspiration (46 %) compared with observation (44.6 %) [7]. Rarely follicular cysts are seen in neonates and give rise to isosexual pseudoprecocity; these usually regress within the first 4 months after birth.

Histopathological Appearances: By definition, follicle cysts are >3 cm in diameter and usually do not exceed 10 cm. Macroscopically they have a smooth surface and thin walls and contain watery fluid. Microscopically follicle cysts typically show an inner lining of several layers of granulosa cells, which may be luteinized, and an outer lining of theca cells (Fig. 2.1a); the two layers can be delineated with a reticulin stain. During involution, the lining becomes thin (Fig. 2.1b) and ultimately may be denuded, especially the granulosa cell layer, in which case the differential diagnosis is with a simple indeterminate cyst. Depending on the extent of luteinization, follicle cysts may be non-luteinized or show luteinization of granulosa cells (granulosa lutein cyst) or theca interna cells (theca-lutein cysts).

Differential Diagnosis: Rarely the differential diagnosis of follicle cysts is with a cystic granulosa cell tumor; these are usually lined by plump

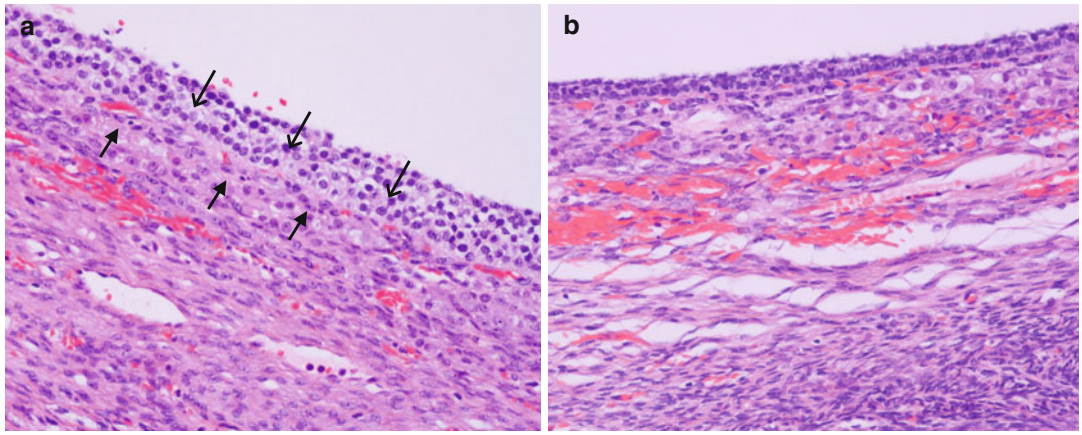

Fig. 2.1 (**a**) Follicle cyst lined by inner layer of granulosa cells (*open arrows*) and outer luteinized theca interna cells (*closed arrows*). (**b**) Follicle cyst showing a thin inner layer of granulosa cells suggesting involution

granulosa cells that are irregularly arranged and are usually multicystic. A possible diagnostic pitfall arises by crosscutting of cystic follicles and misinterpretation of the plump and mitotically active theca cells as a stromal neoplasm.

Corpus Luteum and Corpus Luteum Cysts

In the normal menstrual cycle, corpora lutea are the result of ruptured follicles. Corpus luteum cysts usually occur in women of reproductive age but can rarely occur in neonates [8] or after sporadic ovulation in postmenopausal women. Macroscopically they are recognized by their yellow appearance when recent and as white nodules when degenerating. They arise when excessive hemorrhage delays involution of the corpus luteum after ovulation and may be cystic or hemorrhagic.

By convention, a corpus luteum cyst is generally designated as a cystic corpus luteum that is >3 cm in diameter. Most are asymptomatic, but they may present with menstrual abnormalities or amenorrhea and occasionally rupture giving acute abdominal symptoms [4]. They may also be detected on ultrasound examination in normal early pregnancy. Macroscopically, in common with the smaller cystic corpus luteum, they are yellow in appearance and often filled with altered blood or clear fluid. The size may reach 10 cm diameter. Microscopically corpus luteum cysts are lined by a thick layer of luteinized granulosa cells with an outer layer of smaller luteinized theca interna cells; there may also be an inner layer of connective tissue (Fig. 2.2a). There is a prominent zone of vascularization resulting from the growth of blood vessels growing from the theca into the collapsed granulosa cell layer. The granulosa cells and theca-lutein cells are smaller than those seen in a fresh corpus luteum; nuclei are small and hyperchromatic, and mitoses are not seen. As involution proceeds, there are smaller islands of lutein cells and increasing fibrosis (Fig. 2.2b).

The differential diagnosis includes luteinized follicular cysts which are less likely to be hemorrhagic and also lack the vascularized zone that is seen in corpus luteum cysts. Some follicle-derived cysts may be difficult to classify. Endometriotic cysts may be indistinguishable macroscopically, but the diagnosis is clear on microscopic examination with the detection of endometrial glands and stroma.

Corpus Albicans Cysts

A corpus albicans is usually a solid hyalinized scar but occasionally is cystic with a central cavity that contains clear fluid. These cysts are usually <1 cm diameter and are lined by a band of hyalinized fibrous tissue. They are asymptomatic.

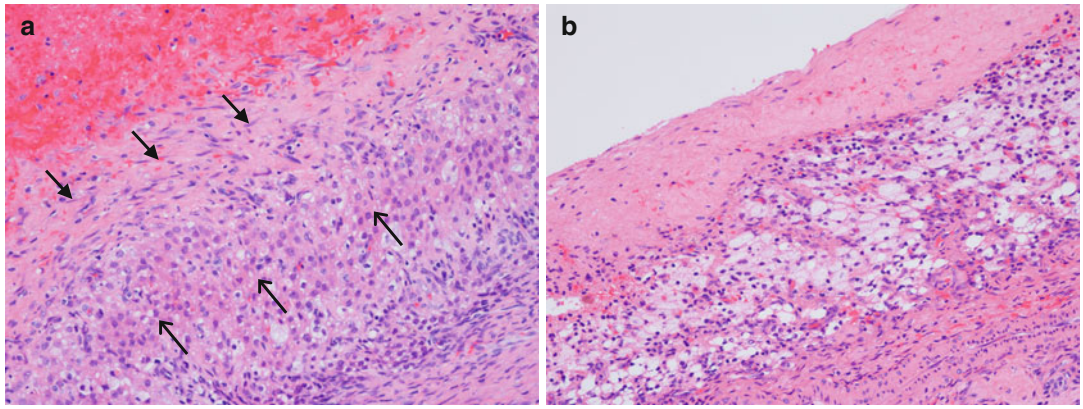

Fig. 2.2 (**a**) Early corpus luteum cyst with organizing hematoma and lining of fibrous tissue (*closed arrows*) and luteinized cells (*open arrows*). (**b**) Late corpus luteum cyst with an inner layer of fibrous tissue and vacuolated involuting luteinized cells

Polycystic Ovarian Syndrome

Introduction: Polycystic ovarian syndrome (PCOS; previously Stein-Leventhal syndrome) is a common cause of infertility. It is the most common endocrine disorder in women, with a prevalence of 6–10 % based on US National Institutes of Health criteria and as high as 15 % based on the broader Rotterdam criteria [9, 10]. Definitions of PCOS vary and more recently have been based on clinical features, rather than the morphological features of polycystic ovaries. Definitions take into account features of oligo- or anovulation; clinical or biochemical hyperandrogenism, for which other etiologies have been excluded; and polycystic ovaries, diagnosed by ultrasound. A 2003 consensus workshop sponsored by ESHRE/ASRM in Rotterdam [11, 12] agreed PCOS to be present if any two of the following three criteria were met, provided other causes were excluded: oligo-ovulation and/or anovulation, excess androgen activity, and polycystic ovaries. Other common features observed in PCOS are obesity and insulin resistance, with or without associated diabetes, but these are not part of the diagnostic criteria. PCOS represents a spectrum of features with some cases having less severe manifestations, and many women with polycystic ovaries have less pronounced metabolic alterations. Women with amenorrhea, androgenic manifestations, and enlarged polycystic ovaries represent the severe end of the spectrum.

Pathogenesis: The pathogenesis of PCOS is not clear. The syndrome is often familial, suggesting involvement of hereditary factors, but the specific mode of inheritance has not been determined [13, 14]. Multiple biochemical pathways are implicated in the pathogenesis of PCOS, and hence a wide range of genes have been investigated, including genes of steroid hormone metabolism, gonadotropin release and action, insulin secretion and action, adipose tissue metabolism and genes encoding inflammatory cytokines. Nevertheless, to date, no clear gene associations have been detected, and none of these genes appear to play a key role in the etiology and pathogenesis of PCOS. It is likely that environmental and genetic factors interact and that PCOS is inherited as a complex, polygenic trait [15, 16]. The determination of the genetic factors that predispose to PCOS is hampered by the low fecundity of affected females, the lack of a male phenotype, the absence of a good animal model, and until recently the lack of consensus on the diagnostic criteria.

The pathophysiology of PCOS is complex and not completely understood. It is likely that many interlinked mechanisms play a role in the initiation and/or perpetuation of PCOS [17, 18]. Some patients with PCOS have the HAIR-AN syndrome of hyperandrogenic-insulin-resistant-acanthosis nigricans. This syndrome can be separated into insulin-resistant and nonresistant

types; the insulin-resistant type has PCOS and increased LH, whereas the nonresistant type has stromal hyperthecosis and near-normal LH levels [19]. The HAIR-AN syndrome highlights the complexities of the links between insulin resistance, PCOS, and hyperthecosis.

Clinical Features: By definition, PCOS is not associated with underlying pituitary or adrenal pathology. It is a clinicopathologic syndrome and the presenting features vary with age. PCOS is associated with precocious puberty in children, menstrual disturbances in teenagers, and infertility and glucose intolerance in adults. Obesity exacerbates the insulin resistance and favors progression to diabetes, but whether obesity is a cause or an effect of PCOS is unclear. There is a strong association with subfertility and infertility, and there are various approaches to the management of this clinical problem [20, 21]. Many patients have increased LH levels due to increased LH pulse size and frequency, and these high LH levels lead to excessive thecal growth and hence androgen production. FSH levels are usually normal or low, and the LH:FSH ratio is >2. Women with high LH levels are at highest risk of infertility and miscarriage [22]. Hyperinsulinemia is common.

The ultrasound appearance of the ovary shows at least 10 peripheral cysts, usually <10 mm diameter. There is increased stroma and often the ovarian volume is increased. The ovarian features of PCOS are, however, variable: some women have normal-sized ovaries with minimal microcystic change.

As well as the endocrine and cardiovascular effects, women with PCOS are at increased risk of developing endometrial hyperplasia and endometrial neoplasia, with evidence supporting a 2.7-fold increased risk of endometrial cancer in women with PCOS [9, 10]. Most endometrial neoplasms are type 1 endometrioid adenocarcinoma associated with excess estrogen stimulation, and the prognosis is good.

Histopathological Findings: Wedge resection of the ovary is no longer performed, and therefore polycystic ovaries are usually encountered in routine hysterectomy specimens or very rarely when ovarian excision is necessary to control androgenic features associated with PCOS. Macroscopically, the ovaries are enlarged with multiple bluish translucencies indicating the cystic follicles. On cut section, there are multiple small cysts usually of uniform size, 4–10 mm diameter, arranged peripherally within the cortex. The capsule is usually thickened.

Microscopically there is collagenous thickening of the tunica albuginea, usually around threefold. The follicular cysts are lined by non-luteinized granulosa cells and outer layer of luteinized theca interna cells. Primordial follicles are present. Anovulatory women show minimal features of previous ovulation such as corpora lutea and corpora albicantia, but evidence of ovulation does not preclude the diagnosis. Atretic follicles are present, often surrounded by prominent luteinized theca cells. Some cases show luteinized stromal cells and luteinized hilus cells.

Differential Diagnosis: PCOS is a clinical syndrome, and the diagnosis is not made by the histopathologist. There are various conditions in the clinical differential diagnosis, including hormone-producing ovarian neoplasms. For the histopathologist, the differential diagnosis of the macroscopic and microscopic features is limited. Consideration should be given to ovarian hyperstimulation syndrome and hyperreactio luteinalis in which the ovary shows multiple theca-lutein cysts and prominent luteinized stromal cells, but the clinical situation in both these conditions should minimize confusion.

Stromal Hyperplasia

Introduction: Stromal hyperplasia is defined as an expansion of the cortex and medulla of the ovary by an excess of stromal cells [23]. Mild stromal hyperplasia is a common incidental finding in perimenopausal and postmenopausal women, with mild hyperplasia of ovarian cortical and medullary stroma found in around one third [3]. A morphometric study reported moderate to severe ovarian stromal hyperplasia in one third of women in their sixth and seventh decades, with a significant association with postmenopasual endometrial adenocarcinoma [24]. The distinction from stromal hyperthecosis is based on the

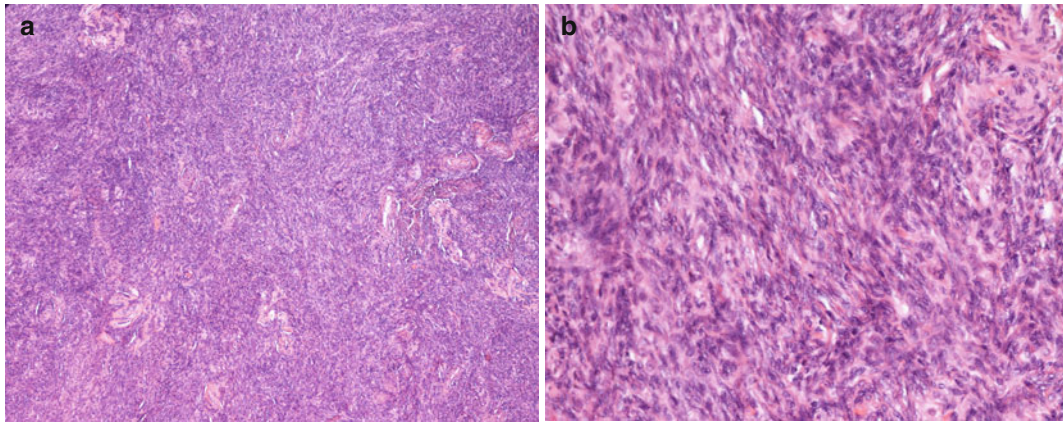

Fig. 2.3 (**a**) Cortical stromal hyperplasia characterized by whorls of spindle cells showing increased cellularity but otherwise resembling those in the normal ovarian cortex. There is loss of the normal corticomedullary interface. (**b**) Higher-power view of cortical stromal hyperplasia

presence of luteinized stromal cells, but small numbers of luteinized cells are often detected after careful searching of the cortex of ovaries with stromal hyperplasia, and these entities are likely to represent a morphological spectrum [23]. As there is little correlation of the severity of stromal hyperplasia with clinical symptoms, it has been suggested that the term stromal hyperplasia should be reserved for definite and florid cases [3]. Minimum criteria suggested for the diagnosis of ovarian stromal hyperplasia are obliteration of the normal distinction between the cortex and medulla or some nodularity to the excessive stroma.

Clinical Features: Most patients are asymptomatic, and stromal hyperplasia is detected as an incidental finding in ovaries removed for other reasons. Some cases have clinical symptoms resulting from androgen secretion by the hyperplastic stroma [25] with peripheral aromatization to estrone and potential effects on endometrium [26]. These features are less common in stromal hyperplasia than in stromal hyperthecosis.

Histopathological Findings: In stromal hyperplasia, the ovaries may be normal in size or are uniformly enlarged up to twice the normal size. The normal surface convolutions seen in postmenopausal ovarian atrophy are less obvious, and the capsular surface is smooth. The cut surface may show only a mild increase in cortical thickening or may show loss of the normal demarcation with a homogeneous tan/brown or whitish/pale yellow surface. Severe cases may show some nodularity.

Microscopically there is loss of the normal defined ovarian cortex with expansion of stromal cells that may occupy the whole ovary (Fig. 2.3a). The process may be diffuse, but more commonly there is a widespread nodular pattern particularly in the cortex. The cells are identical to those normally seen in the ovarian cortex with scanty cytoplasm and little collagen (Fig. 2.3b). Mitoses are not common. Some lesions include macrophages and have an overall "granulomatous" appearance, possibly reflecting regression of luteinized stromal cells [3].

Differential Diagnosis: The differential diagnosis is from ovarian fibroma which, in contrast with stromal hyperplasia, is usually unilateral and endometrial stromal sarcoma which shows the characteristic vascular pattern and mitoses.

Stromal Hyperthecosis

Introduction: Stromal hyperthecosis is defined as the presence of luteinized cells of thecal origin within ovarian stroma distant from the follicles. The luteinized cells may be clustered in groups or distributed singly. Some consider stromal hyperthecosis to be part of a spectrum with stromal hyperplasia,

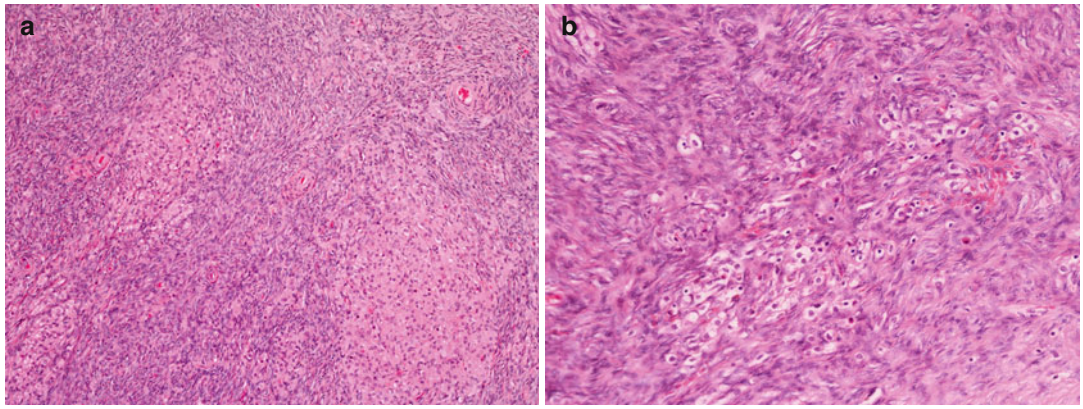

Fig. 2.4 (**a**) Stromal hyperthecosis. This low-power view shows clusters of eosinophilic luteinized stromal cells within hyperplastic ovarian cortical stroma. (**b**) Stromal hyperthecosis. These clusters of luteinized cells show clear cytoplasm and are more diffusely distributed

but other cases merge with PCOS, and there are distinctions in the clinical findings between stromal hyperthecosis and stromal hyperplasia.

Clinical Features: Although hyperthecosis may be asymptomatic in postmenopausal women, usually patients are of reproductive age and have androgenic manifestations [27, 28] and occasionally estrogenic features. Stromal hyperthecosis is one of the most common benign causes of virilization. Testosterone levels may be in the range of androgen-secreting tumors, which need to be considered in the clinical differential diagnosis. As in PCOS, patients may also have obesity, hypertension, and reduced glucose tolerance. Stromal hyperthecosis may be also seen in association with endometrial hyperplasia and endometrial carcinoma. Stromal hyperthecosis may be familial and accompanied by acanthosis nigricans, diabetes, and hyperandrogenism as part of the HAIR-AN syndrome.

Histopathological Findings: Macroscopically both ovaries are enlarged up to 8 cm diameter, although they are usually around twice the normal size. Occasionally the changes are unilateral. The cut surface shows a tan or yellow appearance, with nodularity in severe cases. Microscopically there is hyperplastic ovarian stroma admixed with luteinized cells which form small nests or are scattered singly (Fig. 2.4a). The cells are typically more numerous in the medulla and have abundant clear or eosinophilic cytoplasm, a small central nucleus, and a single conspicuous nucleolus (Fig. 2.4b). The luteinized cells can be highlighted by their immunoreactivity for inhibin and calretinin.

Differential Diagnosis: The high circulating androgen levels may require clinical exclusion of an androgen-secreting tumor. The histopathological differential is from stromal luteoma; an arbitrary size criterion of 1 cm diameter separates stromal luteoma from nodular stromal hyperthecosis.

Hilus Cell Hyperplasia

Hilus cells, also termed Leydig cells, are rounded polygonal cells with eosinophilic cytoplasm and a central vesicular nucleus. They are rarely observed in routine sections of the ovary, and therefore their detection is likely to denote hyperplasia. The definition may be difficult as the hilar cell nests are often widely separated and difficult to quantify without extensive sectioning of the ovaries [29]. Hilus cell hyperplasia is common around the menopause and in pregnancy in response to increased gonadotropin levels. In pregnancy, there may be a nodular proliferation of hilus cells with nuclear enlargement, hyperchromasia, and pleomorphism. In nonpregnant women, hilus cell hyperplasia usually arises in a background of stromal hyperplasia and hyperthecosis. Hilus cell hyperplasia is usually mild and usually not

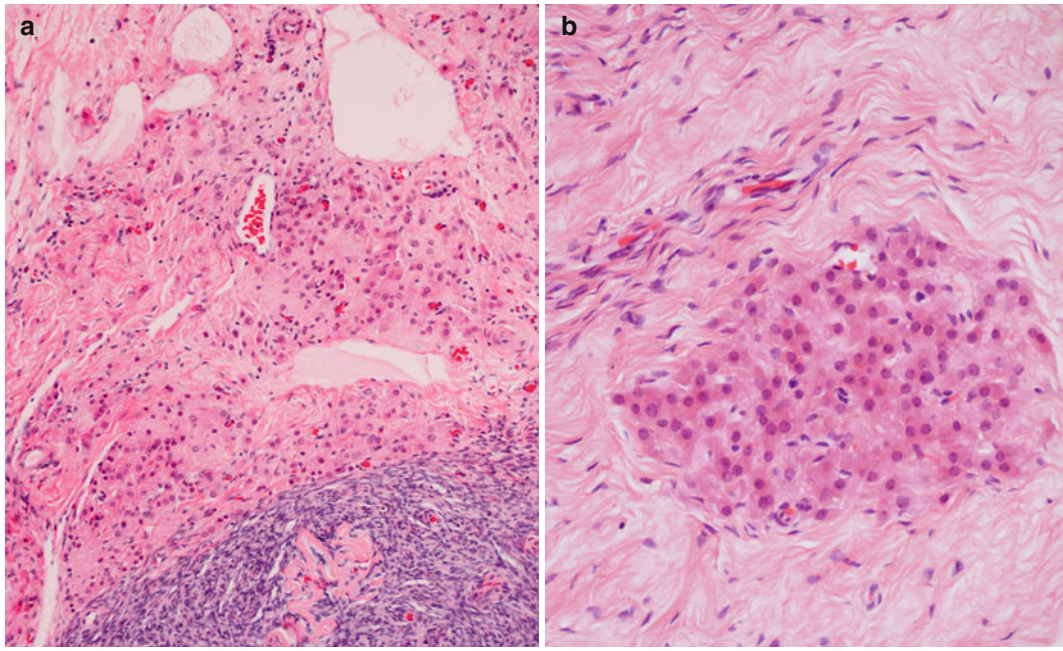

Fig. 2.5 (**a**) Hilus (Leydig) cell hyperplasia. Clusters of eosinophilic hilus cells associated with vessels in the ovarian hilus. This example was associated with stromal hyperplasia. (**b**) Hilus cell hyperplasia. Cluster of hilus cells showing typical eosinophilic cytoplasm, rounded uniform nuclei, and lipofuscin pigment

associated with endocrine disturbance, although severe cases may have virilization and high circulating androgen levels [30].

Microscopically there are clusters of typical hilus cells with eosinophilic granular to finely vacuolated cytoplasm (Fig. 2.5). Intracytoplasmic lipofuscin is often seen, and Reinke crystals may be demonstrable, although they are usually scarce. There is strong immunoreactivity for inhibin and calretinin. The distinction between hilus cell hyperplasia and a hilus cell tumor is arbitrary and based on the formation of a mass lesion [23] or size of <1 cm diameter [29, 31].

Ovarian Pathology During Pregnancy

Introduction

The cells in the ovarian cortex and hilum are highly responsive to circulating gonadotropin and steroid hormones, and this may lead to specific ovarian changes during pregnancy. The recognition of these pregnancy-associated nonneoplastic lesions is important since most will involute after pregnancy and radical surgery is not appropriate.

The corpus luteum of pregnancy is the corpus luteum that was present in the fertilized cycle. It produces progesterone and is critical for maintenance of pregnancy during the first trimester. After this time, the corpus luteum regresses and has a negligible role in pregnancy maintenance in the second and third trimesters. Features that distinguish the corpus luteum in pregnancy are enlargement of the granulosa lutein cells and the presence of cytoplasmic vacuoles (Fig. 2.6) [32]. The importance of the corpus luteum of pregnancy is the recognition of this structure as a potential cause of ovarian mass in the first trimester.

Theca-Lutein Hyperplasia of Pregnancy

Theca-lutein hyperplasia of pregnancy, nodular theca-lutein hyperplasia of pregnancy, and pregnancy luteoma can be considered to form part of

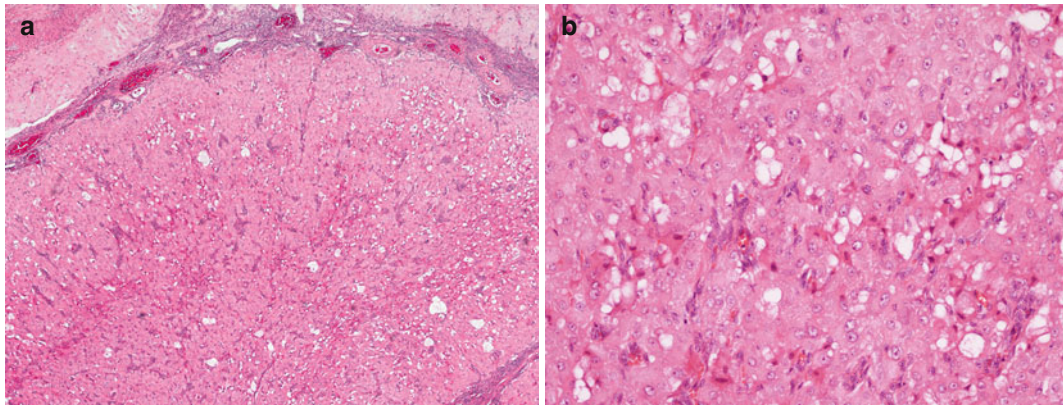

Fig. 2.6 (**a**) Corpus luteum of early pregnancy. Low-power view showing cerebriform contour and enlarged granulosa cells. (**b**) Corpus luteum of early pregnancy. High-power view showing enlarged granulosa cells and cytoplasmic vacuolation

a spectrum of changes in pregnancy, although they are often considered as separate entities. Ovaries removed at the time of delivery will show variable numbers of follicles with an attenuated granulosa cell layer and prominent often asymmetrically expanded luteinized theca. The features are similar to those seen in hyperthecosis and are due to the effects of chorionic gonadotropins on the ovary [33, 34].

Nodular Theca-Lutein Hyperplasia of Pregnancy and Pregnancy Luteoma

Introduction: These are nodular tumorlike masses of lutein cells that develop during an otherwise normal pregnancy. There is expansion of the follicular structures of theca-lutein hyperplasia and coalescence into nodules, with formation of multinodular often multicentric or bilateral nodular tumorlike masses of lutein cells [33, 34]. Although an origin from atretic follicles has been suggested [33], others consider that the luteinized cell nodules may also arise by proliferation of luteinized ovarian stromal cells [3, 29]. Pregnancy luteoma is a more extreme form of nodular theca-lutein hyperplasia but forms part of a spectrum. Pregnancy luteoma is strictly defined as the formation of an expansile solitary brown or yellow tumor that displaces the ovarian parenchyma [23]. Often the ovaries show multiple, multicentric nodules reflecting the spectrum of changes from nodular theca-lutein hyperplasia to stromal luteoma. This spectrum provides evidence that pregnancy luteomas are not true neoplasms, although it is possible that rare solitary pregnancy luteomas could represent clonal proliferation in response to the hormonal environment of pregnancy [33].

Clinical Features: Most patients with pregnancy luteoma have a history of multiple pregnancy and up to 80 % occur in black women [33, 34]. Most are asymptomatic, but they can present with abdominal pain after torsion or with tumor-like masses detected incidentally on ultrasound or at caesarean section. In some cases, pregnancy luteoma leads to virilization, and rarely increased androgen levels may affect a female fetus leading to virilization at birth [35].

Nodular theca-lutein hyperplasia and pregnancy luteoma usually present in the third trimester and involute postnatally. Although beta human chorionic gonadotropin (βhCG) is essential for the development of pregnancy luteomas, this is not the only factor since these lesions do not occur in the first trimester when βhCG levels are highest nor are they seen in association with gestational trophoblastic neoplasia [3].

Histopathological Findings: Macroscopically the ovaries show multiple or single nodules with a soft gray or tan cut surface. Pregnancy luteomas are usually 6–12 cm diameter but have been reported

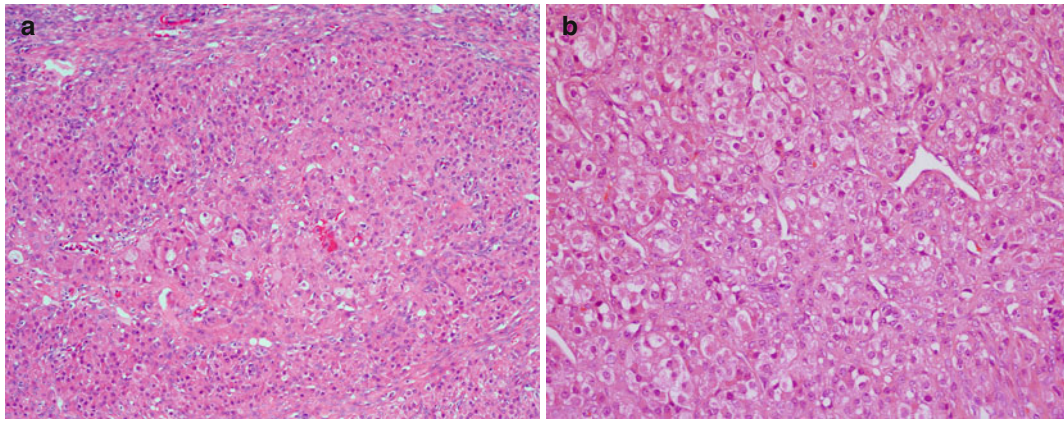

Fig. 2.7 (**a**) Nodular theca-lutein hyperplasia of pregnancy. The ovary shows nodular aggregates of luteinized cells with a well-defined interface with the surrounding stroma. (**b**) Pregnancy luteoma. Cell groups forming clusters interspersed with delicate vessels

to exceed 20 cm diameter. If the ovaries are removed in the puerperium, there may be regression and the cut surface may be soft and necrotic. Microscopically there is prominent luteinized cell proliferation with enlarged, confluent nodules of luteinized cells (Fig. 2.7a). The granulosa cells are usually inconspicuous and attenuated or involuted, and the nodules are formed of luteinized theca cells. The cytoplasm is eosinophilic, and there is a round central nucleus with a prominent nucleolus (Fig. 2.7b). There may be mild nuclear pleomorphism, and scattered mitoses may be seen but <3 per 10 high-power fields. The cells are intermediate in size between granulosa cells and theca-lutein cells. Luteinized cells may also be seen streaming into the stroma, and these may be of stromal rather than follicular origin [23].

Usually the granulosa cells are inconspicuous and may have involuted. However, occasionally the follicles are preserved and expanded and hyperplasia of partially luteinized granulosa cells may be seen [36].

Differential Diagnosis: When multiple, inspection of the ovaries at operation may suggest the presence of nodules of metastatic tumor, and the differential diagnosis in this situation includes metastatic carcinoma and metastatic melanoma. For unilateral pregnancy luteomas, various primary ovarian tumors are in the differential, but the clinical history of pregnancy will usually point to the correct diagnosis. Although thecomas may be luteinized in pregnancy, the basic spindle cell shape is still evident. Sclerosing stromal tumors have a lobular pattern with bands of collagen. Abundant pericellular reticulin is seen in both thecomas and sclerosing stromal tumors. Steroid cell tumors are usually unilateral and usually arise at the ovarian hilus, reticulin surrounds single cells or small groups, and mitotic activity is usually less prominent than in stromal luteomas of pregnancy. Whereas stromal luteomas have relatively little stainable intracytoplasmic lipid, steroid cell tumors show abundant lipid content. Reinke crystals may be seen in Leydig cell tumors. Granulosa cell tumors are rare in pregnancy but when present are often of the juvenile type which may display prominent luteinization and therefore may resemble pregnancy luteoma.

Hyperreactio Luteinalis

In hyperreactio luteinalis, numerous follicular cysts are the manifestation rather than theca cell expansion. In common with nodular theca-lutein hyperplasia, hyperreactio luteinalis (multiple theca-lutein cysts) is also associated with increased βhCG, but, in contrast with pregnancy luteomas, hyperreactio luteinalis is also associated with pathological βhCG elevations. It is associated with hyperstimulation of the ovaries such as in pregnancy [37, 38], especially multiple

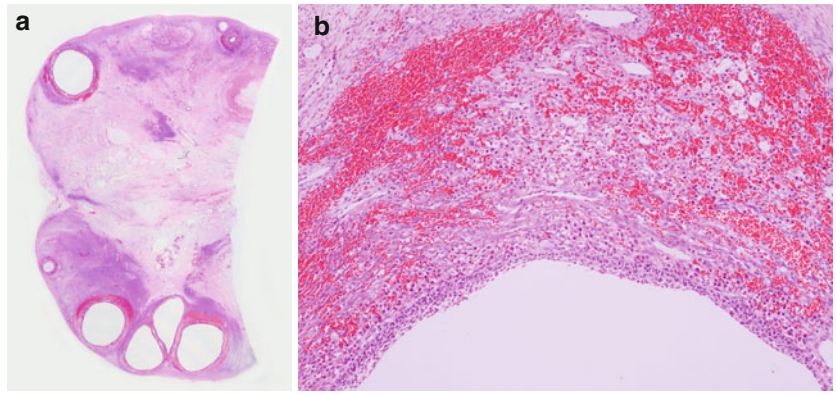

Fig. 2.8 (**a**) Hyperreactio luteinalis. Low-power view showing multiple cystic follicles in an ovary removed at 22 weeks gestational age. (**b**) Hyperreactio luteinalis. Follicle cyst lined by luteinized cells. The adjacent stroma also contains luteinized cells

pregnancies [39], gestational trophoblastic neoplasia, and treatment for ovulation induction [40]. The classical association is with hydatidiform mole and choriocarcinoma, and hyperreactio luteinalis occurs in 25 % of cases. The presentation in the majority of cases is in the third trimester or peripartum period.

Clinical Features: The condition may present as a clinically detectable ovarian mass seen on ultrasound or at caesarean section [40, 41]. Pelvic pain, torsion, and cyst rupture are rare, as is virilization of the mother [42]. The cysts may persist postpartum despite reduced βhCG levels; this may be explained by high LH and FSH levels postnatally if lactation is not established. Regression will occur within a few weeks after parturition but may take up to 6 months [43].

Histopathological Findings: Macroscopically there is bilateral expansion of the ovaries which may reach up to 15 cm diameter. The cut section shows numerous small cysts 1–4 cm diameter that contain yellowish watery fluid or blood. The surrounding stroma is edematous. Microscopically both granulosa cells and theca interna cells may be luteinized, and the follicles may appear hyperplastic (Fig. 2.8).

Differential Diagnosis: Clinical recognition is important to avoid unnecessary surgery during pregnancy with the erroneous clinical impression of malignancy; recognition of this condition will allow conservative management. Solitary luteinized follicular cyst of pregnancy may enter the histopathological differential, but these are solitary and large and granulosa and theca cell layers are not distinct.

Solitary Luteinized Follicular Cyst of Pregnancy and the Puerperium

This is a large distinctive follicular cyst that arises in pregnancy or the puerperium [44, 45]. They usually present in the 3rd and 4th month of pregnancy with a clinically or ultrasound-detected mass, as an incidental finding at caesarean section or in the puerperium. They regress spontaneously after delivery [46]. Hormonal dysregulation is not a feature [47]. The pathogenesis is not known, but stimulation with βhCG is likely to be important.

Macroscopically there is a unilateral unilocular cyst containing watery fluid. The mean size has been reported in one series as 25 cm [47]. Microscopically the cyst is lined by a single layer or multiple layers of large luteinized cells with abundant eosinophilic cytoplasm and large hyperchromatic and pleomorphic nuclei. Mitoses are not seen.

The main differential diagnosis is with a cystic ovarian tumor, particularly in view of the nuclear pleomorphism and hyperchromasia. Awareness of the entity in pregnancy is a major factor in reaching the correct diagnosis.

Ectopic Decidua

The finding of ectopic decidua on the ovarian surface and in the ovarian cortex is common in normal intrauterine pregnancy. When prominent, it forms small nodules on the ovarian surface which, if noted at caesarean section, may cause concern regarding carcinomatosis [48]. The formation of ectopic decidua on the ovarian surface

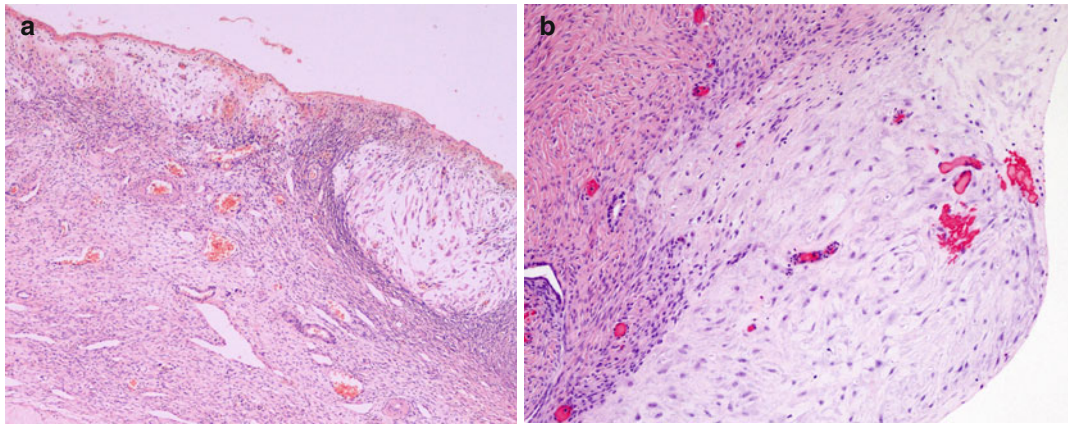

Fig. 2.9 (**a**) Ectopic decidua. Low-power view of decidualization of ovarian subserosa. (**b**) Ectopic decidua. This example was associated with an ovarian adenofibroma

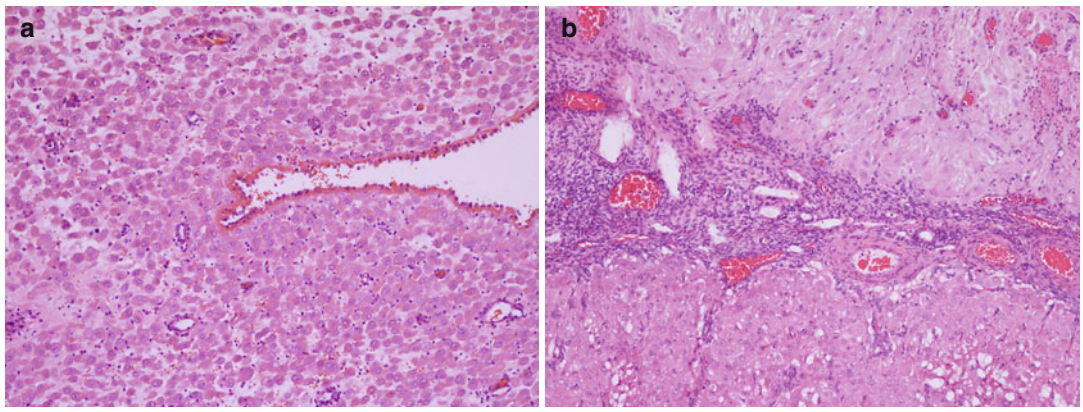

Fig. 2.10 (**a**) Decidualized endometriosis. The ovary was removed at the time of caesarean section performed for placenta accreta. There is prominent stromal decidualization of the endometriotic foci. (**b**) Decidualized endometriosis. Decidualization of ovarian stroma (*top*) in the same case as (a). A corpus luteum is seen in the lower part of the photomicrograph

(Fig. 2.9) and in the cortex is a physiological process arising from the coelomic mesenchyme as a result of progesterone stimulation in pregnancy. It is seen in most pregnancies in the 3rd trimester, but is less common in earlier pregnancy. Decidual change is also seen in endometriotic foci within the ovary in pregnancy (Fig. 2.10).

Macroscopically the ovarian surface shows tan or red spots up to 5 mm diameter. Microscopically the component cells are similar to those seen in decidualized endometrium; the decidualized stromal cells have distinct margins and are polygonal in shape with eosinophilic cytoplasm and a central pale nucleus with prominent nucleolus (Figs. 2.9 and 2.10). As in uterine decidua, there is a prominent leukocyte component, including uterine natural killer cells and macrophages [49]. The main differential is with smooth muscle metaplasia, but the clinical context should ensure a correct diagnosis, which can if necessary be confirmed by immunostaining of decidualized endometrial stromal cells for CD10.

Ovarian Ectopic Pregnancy

Ectopic pregnancy within the ovary is a rare event, occurring only around 1 in 10,000 pregnancies and accounting for 0.94–3.6 % of ectopic gestations [50–54] and up to 6 % of pregnancies

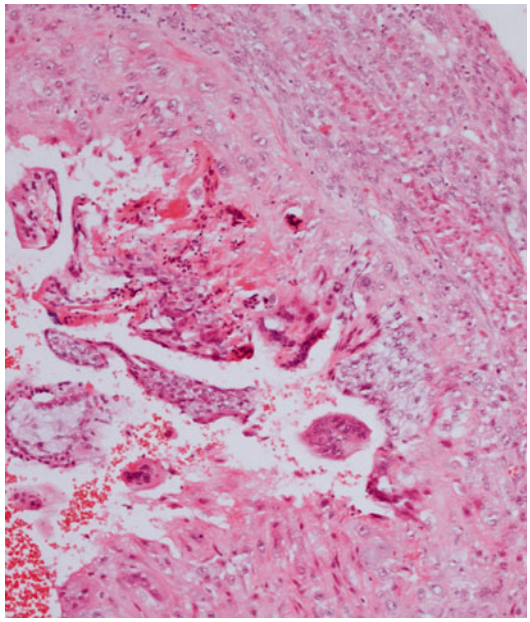

Fig. 2.11 Ovarian ectopic pregnancy. Immature chorionic villi and implantation site are seen with luteinized cells in adjacent stroma

conceived following assisted conception [55]. A definite diagnosis of an ovarian ectopic pregnancy requires exclusion of an ectopic tubal pregnancy with secondary involvement of the ovary. Hence, for a diagnosis of ectopic ovarian pregnancy, the tube must be intact and separate from the ovary; definite ovarian tissue should be present in juxtaposition to trophoblast (Fig. 2.11), and the fetal sac should occupy the normal position of the ovary, with removal resulting in the serum βhCG returning to normal [3]. The relationship between ovarian ectopic pregnancy and use of an IUCD or the presence of pelvic inflammatory disease is not clear with some reporting an association and others not [56]. It is thought that an ovum is likely to undergo fertilization in the fimbria or on the ovarian surface and then implants within ovarian parenchyma.

Inflammatory Conditions

The ovary can be involved in inflammatory processes due to a range of infectious agents, as well as other inflammatory conditions unrelated to infection. The histopathological features in oophoritis due to a range of infections have recently been summarized [57].

Ovarian Inflammation Associated with Infection

Bacterial Infection and Pelvic Inflammatory Disease

Oophoritis due to bacterial infection is usually seen in the context of pelvic inflammatory disease and also involves the fallopian tubes. Recurrent infectious episodes may lead to the formation of a tubo-ovarian abscess, and the inflammatory exudate often leads to the development of adhesions with adjacent structures. Isolated ovarian abscess not associated with salpingitis is uncommon and is usually associated with a predisposing factor such as a recent gynecological operation, childbirth, or complication of intrauterine contraceptive device (IUCD) use. Occasional infections of the ovary arise as a result of spread from intestinal infection such as appendicitis or diverticulitis or a postoperative infection. Whereas oophoritis and abscess associated with PID tend to be insidious, that occurring in isolation may present acutely and require surgical intervention with peritonitis and pelvic abscess as possible sequelae [57].

The presenting features in infectious oophoritis are usually those of pelvic inflammatory disease with pain, fever, and vaginal discharge and sometimes urinary symptoms. In advanced disease, there may be development of a tubo-ovarian mass, and adhesions are a common consequence. The rupture of an abscess occasionally leads to secondary peritonitis or fistula formation, and occasionally healing of an abscess leads to the formation of a cystic structure that can be confused with a simple cyst. Subclinical infections are common, and a history of PID is present in only 50 % cases with tubo-ovarian abscess [58].

Macroscopically there may be a tubo-ovarian mass and abscess formation, often in continuity with the fallopian tube. Milder cases may be limited to showing peri-oophoritis. Rarely in a recurrent infection, a chronic abscess forms

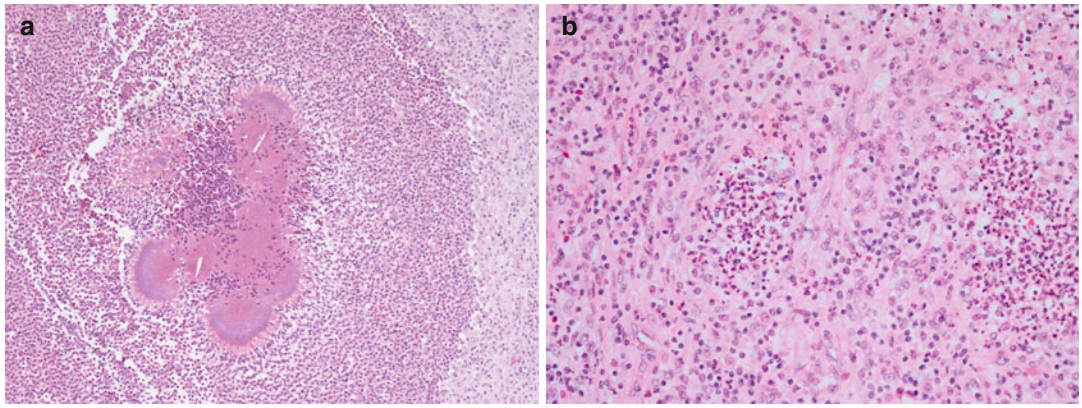

Fig. 2.12 (**a**) Actinomycosis. A colony of actinomyces ("sulfur granule") surrounded by an acute inflammatory cell infiltrate in a case of actinomycosis associated with a tubo-ovarian mass. (**b**) Actinomycosis. Detail of inflammatory infiltrate consisting of neutrophil polymorphs and foamy macrophages admixed with lymphocytes and plasma cells

with the development of a yellow solid mass, termed xanthogranulomatous oophoritis [59]. Microscopically there are the usual features of acute inflammation with neutrophil polymorphs, edema, and vascular dilatation. Abscess formation is usually in continuity with the fallopian tube and may result in permanent loss of ovarian parenchyma. Peri-oophoritis shows neutrophils and fibrin with formation of granulation tissue and sometimes prominent mesothelial proliferation. Rarely an abscess may evolve into xanthogranulomatous oophoritis with accumulation of macrophages, multinucleated giant cells, plasma cells, neutrophil polymorphs, and fibrosis [60].

Actinomycosis

Actinomycosis is uncommon, and most cases occur after prolonged use of an IUCD [61–64]. Despite this association, most cases of IUCD-associated PID are not due to actinomycosis [63]. The organism may be identified in cervical smears of IUCD users, and a substantial proportion of those with positive smears will develop clinical actinomycosis infection and tubo-ovarian abscess [65]. Rarely actinomycosis is not associated with IUCD use [66].

Macroscopically there is a large tubo-ovarian mass which can be unilateral or bilateral and in some cases may mimic pelvic malignancy [67]. Sectioning shows multiple abscesses involving the fallopian tube and ovary and separated by dense scar tissue. The characteristic sulfur granules may rarely be visible macroscopically.

Microscopically there is a nonspecific inflammatory response with neutrophils, foamy histiocytes, lymphocytes, and plasma cells (Fig. 2.12). Bacterial colonies are identified as branching filaments with a basophilic central zone with more peripheral palisading zones appearing eosinophilic (Fig. 2.12). The organisms are Gram positive and also stain with silver stains.

Tuberculosis

The ovaries are only involved in 10 % cases of tuberculosis of the female genital tract, whereas the fallopian tubes are involved in almost all cases. Although most genital tuberculosis is thought to be blood-borne, fewer than 50 % cases have a history of tuberculosis or an abnormal chest x-ray [57]. Ovarian tuberculosis usually results from direct spread from the fallopian tubes, which are almost always involved. There is obliteration of the normal anatomical relationship between the fallopian tube and ovary [23]. Less commonly spread may occur from the gastrointestinal or urinary tract via lymphatics. The intraoperative appearance may mimic ovarian cancer [68, 69]. Microscopically the histological features are similar to those observed elsewhere in the body, although there is rarely caseation in the ovary and the granulomatous inflammation is often confined to the ovarian cortex. Culture or

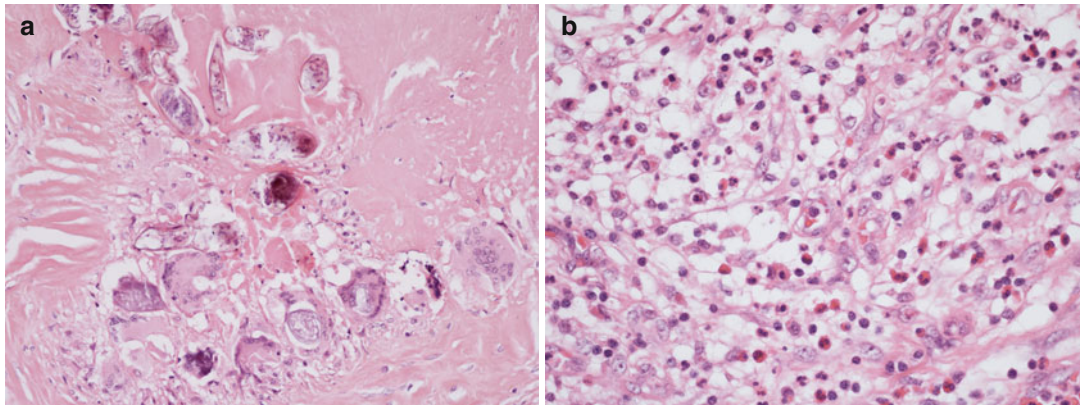

Fig. 2.13 (**a**) Tubo-ovarian schistosomiasis. Degenerate and calcified schistosoma ova surrounded by dense scarring. (**b**) Tubo-ovarian schistosomiasis. Detail of eosinophil-rich inflammatory cell infiltrate

polymerase chain reaction may be helpful to confirm the diagnosis.

Viral Infections

Mumps

Oophoritis may occur in mumps infection, although it is a less common manifestation of this infection than mumps orchitis in males, with estimates of around 5 % of females suffering mumps infection [29, 57]. The histopathological features of mumps oophoritis have not been described.

Cytomegalovirus

Cytomegalovirus can also affect the female genital organs, usually secondary to viremia. Oophoritis is rare and has been reported only in immunocompromised patients [70, 71]. On microscopy infected stromal and endothelial cells are readily identified by their enlargement and pleomorphism and by the characteristic intranuclear inclusions. Immunohistochemistry may help to confirm the diagnosis [72].

Parasitic Infection

Schistosomiasis

Parasitic infections of the ovary are rare, but ovarian schistosomiasis is commonly seen in endemic areas [73]. The worms can gain access to the genital tract via venous anastomoses such as between mesenteric and ovarian veins. Ovarian schistosomiasis may be an incidental finding with normal-sized ovaries, but patients may have pelvic pain or pelvic mass and occasionally irregular menstrual cycle or infertility. The intraoperative findings may be of an enlarged ovary and fallopian tube with abscesses, adhesions, and necrosis and can simulate a malignant tumor. Microscopically there are schistosoma ova surrounded by a granulomatous infiltrate, which usually contain eosinophils as well as lymphocytes, plasma cells, and foreign body giant cells (Fig. 2.13). The inflammatory response may be predominantly eosinophilic. The peripheral zones show fibrosis that increases in amount as the lesions progress and may replace them. Dead ova often undergo calcification. Schistosoma ova can be identified and differentiated by their spines; *Schistosoma haematobium* has a terminal spine, while *S. mansoni* has a lateral spine as does *S. japonicum*, although the lateral spine is less prominent. *S. haematobium* preferentially involves the lower genital tract, whereas *S. mansoni* has a predilection for fallopian tubes and ovaries [57].

Enterobiasis

The involvement of the ovarian surface or rarely parenchyma by *Enterobius vermicularis* is usually an incidental finding [74, 75]. On reaching the peritoneal cavity, the worms die and the ova are released and stimulate an inflammatory response. The granulomas, which contain eosinophils, are localized in the pelvis and may involve the ovarian serosal surface or parenchyma [76]. *Enterobius* ova are smaller than those of schistosoma and lack spines.

Echinococcus

This is an infestation by the cestode *Echinococcus granulosus*, and there are several reports in the literature documenting rare cases of ovarian involvement [77–80]. Ovarian involvement may represent primary or secondary infection and presents clinically or on ultrasound examination as ovarian cysts. The cystic mass may mimic an ovarian cystic neoplasm ovarian cystic neoplasm or endometriosis [80]. The histopathological features are those of a typical hydatid cyst with reports of cysts measuring up to 16 cm diameter. The cysts have a characteristic lining and regress after death of the parasite; cyst wall calcification after regression may be a useful radiological sign.

Fungal Infection

Fungal infection of the ovary is extremely rare even in the presence of disseminated disease. Ovarian involvement by blastomycosis [81, 82] and coccidioidomycosis [83] has been reported, and a case of aspergillus has been reported in an IUCD user [84].

Noninfectious Inflammatory Conditions of the Ovary

The ovary can be affected in a range of noninfectious inflammatory diseases associated with granulomatous inflammation. Sarcoidosis has been reported to rarely involve the female genital tract and may affect the uterus and adnexae [85]. Granulomas are distributed throughout the ovary and are usually an incidental finding. The ovary is also rarely involved by Crohn's disease [86, 87], usually by direct extension of the inflammation from the affected bowel.

Giant cell arteritis may affect smaller arteries and arterioles, and the female genital tract can be affected [88]. Female genital tract involvement in polyarteritis nodosa is most common in the cervix but occasionally affects adnexae [89]. Rarely the ovary shows necrotizing arteritis with no underlying cause [90]. These are considered to be cases of isolated visceral necrotizing vasculitis; systemic disease should be sought, but follow-up rarely uncovers any underlying explanation [90, 91].

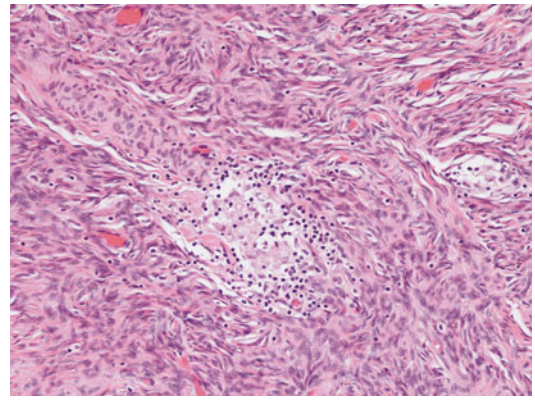

Fig. 2.14 Cortical granulomas. Well-circumscribed granulomas consisting of epithelioid cells and lymphocytes in the ovarian cortex of a postmenopausal woman

Cortical granulomas are seen in 10–15 % of postmenopausal ovaries, usually in association with stromal hyperplasia and hyperthecosis, and it is possible that they represent transitional stages in the involution. The granulomas are circumscribed and show epithelioid cells and lymphocytes, and sometimes multinucleate giant cells and fat crystals (Fig. 2.14). Older lesions are fibrotic and hyalinized.

A granulomatous response to foreign material such as suture material, lipid contrast material, and keratin may be seen in the ovary and can mimic a malignant tumor [92]. Foreign body inflammation in response to bowel contents has also been reported in colo-ovarian fistula [93].

Isolated noninfectious granulomas typically occur in premenopausal women without evidence of systemic granulomatous disease or granulomatous genital tract infection. In most patients, there is a history of surgery involving the affected ovary months or years before, suggesting that the lesions represent a reaction to trauma or tissue necrosis. The lesions resemble the necrobiotic rheumatoid-like granulomas that are found in the cervix after loop excision of the transformation zone [86].

Autoimmune Oophoritis

Premature ovarian failure can be divided into four broad etiological categories: genetic, autoimmune, iatrogenic, and environmental [94].

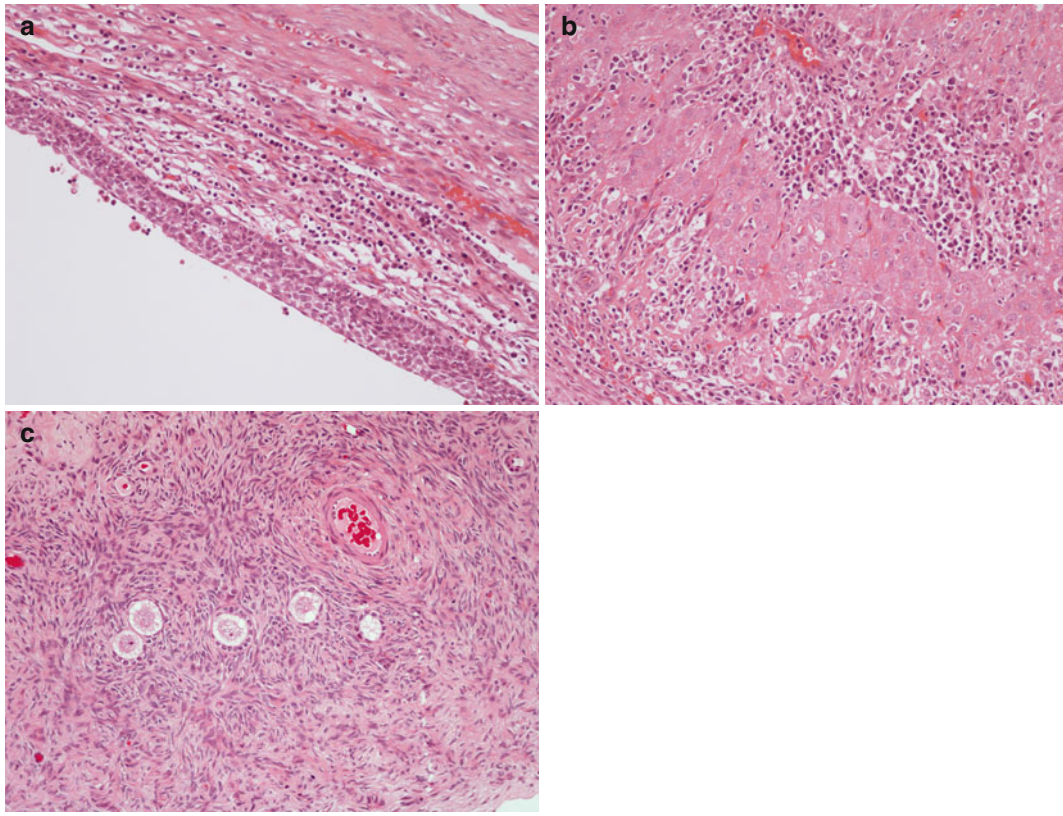

Fig. 2.15 (**a**) Autoimmune oophoritis. Cystic follicle showing lymphocyte infiltrate in the theca interna. (**b**) Autoimmune oophoritis. Intense lymphocyte infiltrate in a fresh corpus luteum. (**c**) Autoimmune oophoritis. Sparing of primordial follicles

There is a strong association between premature ovarian failure and a range of autoimmune disorders [95–98]. A presumed mechanism is the presence of autoantibodies directed against steroid-producing cells, and these can be detected in various autoimmune diseases, especially thyroid and adrenal disease [99]. However, some patients with the clinicopathological features of autoimmune oophoritis do not have anti-ovarian antibodies [100]. Studies of mouse models of the disease have suggested that there is an immune defect, including a reduction in natural killer cell activity, allowing the development of organ-specific autoimmunity and that there is an ovarian target under attack. However, as yet the specific immune defect or the ovarian target is not fully understood [101, 102].

Autoimmune oophoritis usually presents as hypergonadotropic ovarian failure with primary or secondary amenorrhea and premature menopause and infertility [103]. Laboratory studies may confirm the presence of anti-ovarian antibodies, and some patients will have a history of other organ-specific autoimmune disease.

Macroscopically the ovaries are normal in size or enlarged by cystic follicles. On microscopic examination, there is an inflammatory cell infiltrate directed at follicular cells. The infiltrate usually consists of lymphocytes and plasma cells, but sometimes there is an eosinophilic infiltrate or a granulomatous inflammatory response [103–105]. The inflammatory infiltrate is closely related to the theca interna of developing follicles, and the more advanced the follicular development, the denser the inflammatory infiltrate. The granulosa cells are only sparsely infiltrated by inflammatory cells, and primordial follicles are spared (Fig. 2.15). The intervening stroma is normal.

The differential diagnosis includes other causes of oophoritis, but the perifollicular distribution of the inflammation is characteristic.

Endometriosis

Introduction

Endometriosis is defined as the presence of functional endometrial tissue located outside the endometrial cavity. It mainly affects women in their reproductive years, although postmenopausal women may be affected, usually associated with exogenous or endogenous hormone production. The incidence is uncertain, but estimates are that around 10 % of women of reproductive age are affected [106, 107], although this may be an underestimate since the diagnosis may be made only several years after onset of symptoms [108].

Factors that have been associated with endometriosis are Caucasian or Asian race, although more recent studies have cast doubt on the importance of racial factors [109]. Other factors suggested to be associated with an increased risk of endometriosis are lower BMI at age 18 years, long cycle length, reduced parity, and use of IUD, whereas oral contraceptives were protective [110]. There is some indication that genetic factors play a role since the incidence is higher in monozygotic than dizygotic twins [111].

Clinical features vary and include infertility; lower abdominal, pelvic, and back pain; dyspareunia; and dysmenorrhea, but only 5 % of women have all four major symptoms. Many women are asymptomatic, and in one study asymptomatic endometriosis was detected in 40 % of women undergoing laparoscopic tubal ligation [112]. The clinical features correlate poorly with disease extent; women with minimal disease may have severe pain, and those with extensive disease may have relatively few symptoms [113]. Rare complications are formation of a pelvic mass, ascites, hemoperitoneum, and infection or rupture of an endometriotic cyst.

Various theories have been put forward to explain the pathogenesis and pathophysiology of endometriosis [reviewed in [114]]. These include coelomic metaplasia, the induction theory, mullerianosis, and benign metastasis. A more recent proposal suggests that extrauterine stem or progenitor cells that originate from the bone marrow may differentiate into endometrial tissue [115]; candidates are mesenchymal progenitor cells and endothelial progenitors. The most popular theory of retrograde menstruation proposes that the endometrium is shed into the peritoneal cavity at menstruation, implants, and grows into endometriotic foci. There is strong evidence for retrograde menstruation: menstrual blood is found within the peritoneum in over 90 % of women at the time of menstruation; the anatomical distribution of endometriotic lesions is in keeping with retrograde menstruation; and outflow obstruction in vivo due to congenital abnormalities or induced experimentally predisposes to endometriosis. Retrograde menstruation cannot, however, explain the development of endometriosis since this occurs as a normal feature in menstruating women. Endometrial fragments must differ in their ability to survive and grow in women who develop endometriosis and those who do not, and various active areas of research are focusing on this area.

Ovarian Endometriosis

The frequency of sites affected by endometriosis depends on whether diagnosis is based on clinical or histological findings [116]. Clinically the two most frequent sites are the uterosacral ligaments and the ovaries, with other sites in the pelvis accounting for the majority of others, including the pouch of Douglas, pelvic peritoneum, uterine serosa, and fallopian tubes [117]. Endometriosis is often encountered incidentally in bilateral salpingo-oophorectomy samples removed for unrelated reasons, and ovarian endometriosis is the most common site where endometriosis is seen by histopathologists [118]. Extrapelvic disease is seen in 5–12 % of patients clinically, with the intestines the most commonly involved site.

Macroscopic Findings: Ovarian endometriosis has several different patterns which may coexist. Endometriotic lesions on the ovarian surface may be yellow/red lesions in their early stages, bluish/black due to bleeding, brownish yellow due to the presence of hemosiderin, or whitish due to fibrosis and scarring in old lesions. Endometriotic lesions increase in size as they become older, and there may be associated dense

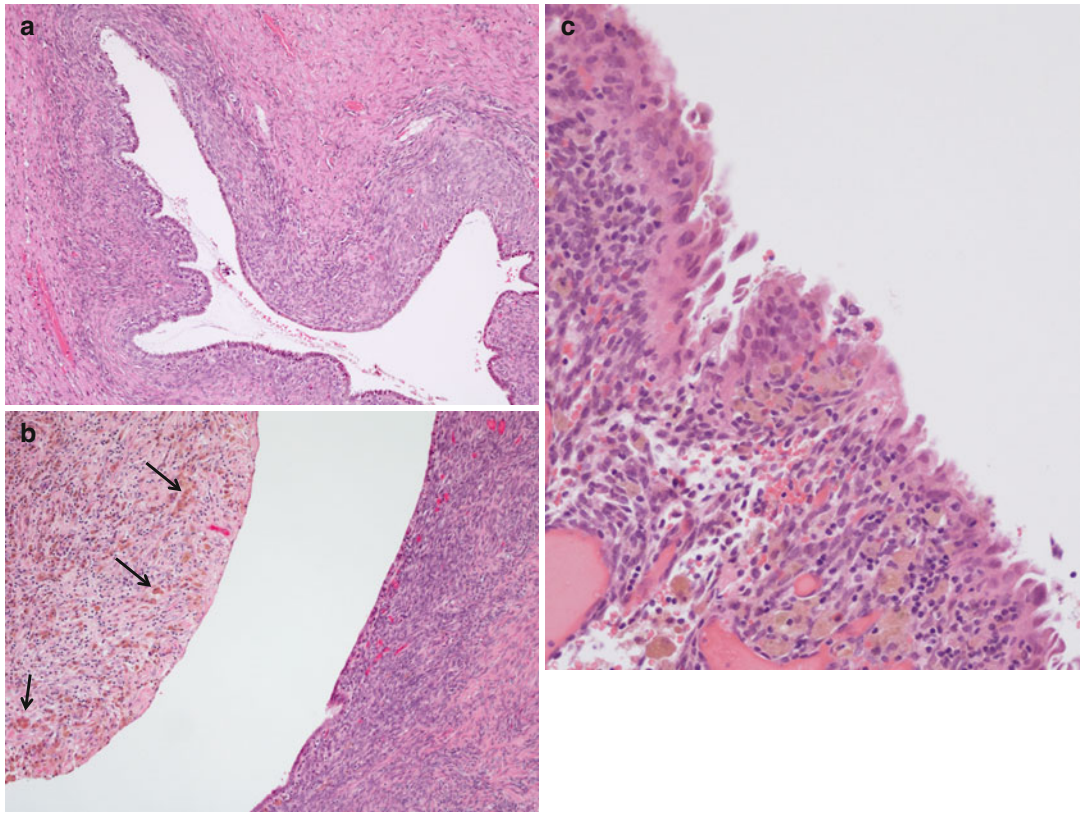

Fig. 2.16 (**a**) Ovarian endometriosis. Typical focus of endometriosis showing easily recognizable endometrial glands and stroma. The stroma was strongly immunoreactive for CD10. (**b**) Ovarian endometriosis. Two sides of an endometriotic cyst. The right side is easily recognizable as endometriosis, whereas the left side shows loss of the epithelium and substantial replacement of the stroma by hemosiderin-laden macrophages (*arrows*). (**c**) Ovarian endometriosis. Reactive atypia in ovarian endometrioma

fibrous adhesions. Cortical endometriosis may have a similar macroscopic appearance, but small lesions may not be visible macroscopically.

The typical endometriotic cyst or endometrioma is a common cause of an ovarian mass in the fourth and fifth decades [119]. The size ranges from a few mm up to >15 cm diameter. The contents are watery or hemorrhagic, and inspissated old blood accounts for the term "chocolate cyst." The cyst wall is of varying thickness and is usually fibrotic [120] with a smooth or shaggy brown lining. Patches of discoloration may be present due to hemorrhage or hemosiderin deposition, and rarely the cyst lining has a cobblestone pattern associated with stromal decidualization within the endometriotic lesions. Endometriotic cysts are associated with hemorrhage, inflammation, and adhesions, which may result ultimately in the formation of a complex ovarian mass which requires careful sampling to exclude malignancy. Because of their complex appearance, endometriotic cysts may be mistaken for malignancy on ultrasound examination, an impression which may be reinforced by a moderately raised CA125 level, a common finding in endometriosis. Since endometriosis has an association with malignancy, any intraluminal polypoid lesions or mural nodules in endometriosis require careful sampling. Endometriotic cysts are often bilateral, and microscopic endometriosis is often detected in the contralateral ovary.

Microscopic Findings: Microscopically, the classical hallmarks of endometriosis are the presence of endometrial glands and stroma (Fig. 2.16a). There is usually evidence of previous hemorrhage with hemosiderin deposition in stromal macrophages. The endometrial glands may be inactive or have features of proliferative or secretory activity. The stromal component

resembles endometrial stroma with a typical network of arterioles. These typical and easily recognizable features, however, represent a minority of cases, and endometriotic cysts often present as a fibrous-walled cyst with a rather indistinct lining. The stroma may be inconspicuous and form only a thin cuff. Sometimes the typical endometrial stroma may be obscured by macrophages, or in long-standing lesions the stromal cells may appear more fibrotic (Fig. 2.16b). The presence of hemosiderin-laden macrophages may be a helpful feature, along with the presence of arterioles similar to those seen in the endometrium. The stroma may also undergo metaplastic changes, particularly smooth muscle metaplasia. The lining epithelium may be attenuated and nondescript, and sometimes a definite diagnosis cannot be made. Metaplastic changes may also occur in the epithelium, including tubal, hobnail, and rarely mucinous and squamous metaplasia.

Epithelial cells may show atypia characterized by nuclear enlargement and hyperchromasia with abundant eosinophilic cytoplasm (Fig. 2.16c). These changes are regarded as reactive in most cases with no associated increased risk of malignancy [121], although occasionally the changes merge with neoplasia within a cyst, suggesting premalignant potential in rare cases [122]. In the presence of pregnancy or after high-dose progesterone treatment, foci of endometriosis may show prominent decidualization which may lead to confusion with a corpus luteum or xanthomatous change. Unusual histological features are the presence of a xanthomatous nodule lacking typical endometrial glands, which are considered to represent burnt-out endometriotic foci. Stromal endometriosis is endometriosis that lacks the epithelial element and has been reported at several sites [123] and may occur within the ovarian cortex.

The diagnosis of endometriosis may be difficult. The endometrial lining epithelium may be attenuated and cuboidal in appearance and if atrophic may resemble a simple cystadenoma lining. Endometrial stroma may be minimal, but even a minute amount can identify the cyst as endometriotic. Immunostaining for CD10 may help highlight endometrial stroma in subtle lesions, although it is important to recognize that this antibody is not specific for endometrial stroma. In rare cases, the endometrial lining of an endometriotic cyst is completely lost, and the stroma has been effaced by repeated hemorrhage. The residual appearance may be of hemosiderin-laden macrophages within a fibrous wall, and in this situation the diagnosis cannot be made with certainty.

Differential Diagnosis: The differential diagnosis of ovarian endometriosis includes ovarian inclusion cysts and glands, but these lack the typical surrounding endometrial stroma, although this can be subtle. Inclusion cysts are usually lined by cuboidal or ciliated cells rather than endometrial cells and may be associated with psammoma bodies. The presence of macrophages and hemosiderin deposition suggests endometriosis, and CD10 immunoreactivity may help to clarify the diagnosis of endometriosis. Some apparent cortical inclusion cysts may show ill-defined weaker reactivity for CD10, and the diagnosis may be impossible to determine with certainty [23]. Rete ovarii may superficially resemble endometriosis, but the glands have a characteristic ramifying pattern, are lined by cuboidal or columnar cells and are surrounded by condensed ovarian stroma rather than endometrial stroma.

Other rare differential diagnoses include extrauterine stromal sarcoma versus stromal endometriosis, but the latter rarely forms masses and lacks stromal mitotic activity and vascular invasion. Corpus luteum cysts may be confused with endometriosis both macroscopically and microscopically since both may show a ragged internal surface and hemorrhage, but endometrial glands and stroma are absent, and corpus luteum cysts usually contain aggregates of luteinized theca cells.

Development of Malignant Change in Endometriosis

Ovarian endometriosis may undergo similar changes to those seen in the endometrium. Formation of endometrial polyps gives rise to polypoid endometriosis, and endometriotic lesions at any site may undergo hyperplasia ranging from simple hyperplasia to atypical complex hyperplasia.

The incidence of malignancy in endometriosis is uncertain. Florid endometriosis may form tumorlike masses which can be confused with a malignant tumor clinically and macroscopically. A malignant tumor arising in endometriosis may lead to destruction of the associated endometriosis or extensive sampling may be necessary to detect the endometriosis from which the tumor has arisen. The incidence of malignant tumors arising in ovarian endometriosis is cited as 0.3–0.8 % by some authors, but others have detected higher levels of 1.1–3 % [118, 124]. The variation in incidence is likely to reflect differences in sampling and the precise criteria used to determine whether a malignant tumor has arisen in endometriosis. Endometrioid carcinoma accounts for the majority of cases (70 %) and clear cell carcinoma for 4 %. However, although endometrioid carcinoma is the most common tumor type in endometriosis, the association with clear cell carcinoma is stronger with 25–50 % cases being associated with endometriosis. Other rarer tumors that may arise are borderline endometrioid adenofibromas, stromal sarcoma, squamous cell carcinoma, and carcinosarcoma.

Miscellaneous Lesions

Surface Epithelial Inclusion Cyst

The normal ovarian surface epithelium is a single layer of modified mesothelial cells. Invagination of the ovarian surface epithelium results in glandular structures within the ovarian cortex, and these may develop into inclusion cysts. Ovarian inclusion cysts are thought to arise as part of the healing reaction after follicular rupture, but they could also result from entrapment in surface adhesions. The frequency of inclusion cysts increases with age, and they are common in late reproductive age and postmenopausal women. They are asymptomatic and detected as an incidental finding.

Macroscopically inclusion cysts are often multiple and scattered in the cortex, although rarely may involve the medulla. By convention they are <1 cm diameter, larger cysts being considered to be cystadenomas. Microscopically

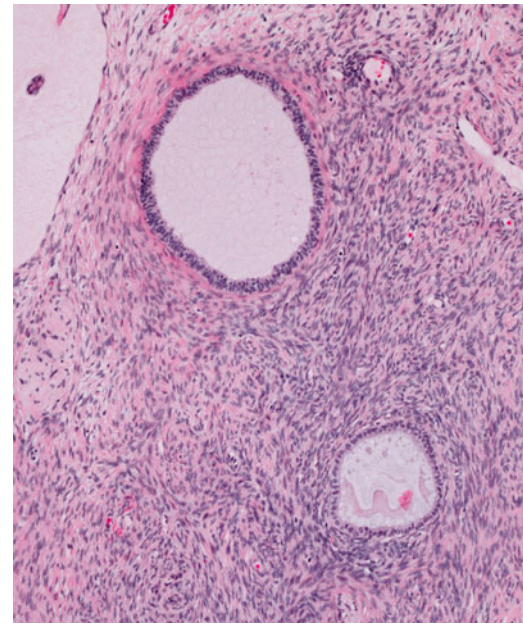

Fig. 2.17 Cortical inclusion cyst. Cyst lined by cuboidal epithelium within the cortex of an ovary from a postmenopausal woman

inclusion cysts are lined by nonspecific flattened or cuboidal epithelium (Fig. 2.17) or benign tubal-type ciliated epithelium [125]. Psammoma bodies may be seen in the cysts or in adjacent stroma. Less commonly the cysts are lined by epithelium of other Mullerian type such as mucinous endocervical-type or endometrial-type epithelium. The differential diagnosis includes atrophic endometriosis.

Inclusion cysts are found in the majority of ovaries from postmenopausal women. Their importance arises from the role of inclusion cysts in the development of surface epithelial neoplasms. This conclusion was based on the detection of increased numbers of surface inclusion cysts in the contralateral ovary of women with ovarian cancer compared with controls. In addition, occasionally inclusion cysts show dysplastic changes and immunoreactivity for a range of epithelial ovarian tumor markers. More recent evidence has, however, suggested alternative origins, and the relative contributions to the pathogenesis of epithelial ovarian cancer between ovarian cortical inclusion cysts, fallopian tube, endometrium, and peritoneum remain unclear [125–127].

Rete Cysts

The rete ovarii is the ovarian analogue of the rete testis and is present in the hilus. There is a network of branching tubule lines by the epithelium which is flattened, cuboidal, or columnar, and there is a stromal cuff of ovarian type stroma. Occasionally the rete may develop into a hilar cyst or, if >1 cm diameter, a cystadenoma. These are usually unilocular and have been reported to have a mean diameter of 8.7 cm (range 1–24 cm) [128]. The lining epithelium is a single layer of non-ciliated epithelium. Clues to the origin are the hilar location, presence of muscle, hyperplastic hilus cells within the wall, and an irregular inner lining.

Simple or Indeterminate Cysts

The precise nature of some ovarian cysts may be impossible to determine with certainty. The lining epithelium may be attenuated and nonspecific resembling epithelial or mesothelial cells, or the epithelium may be lost by trauma or desiccation. The cyst contents are usually nonspecific and watery. Additional sampling may allow more definitive identification of a cyst as serous or endometrioid, and other features such as hemosiderin-laden macrophages within the wall may suggest a specific diagnosis, such as endometriosis or hemorrhagic corpus luteum cyst. A rare additional possible cause of a nonspecific cyst is a cystic struma ovarii with inconspicuous thyroid follicles within the wall, a diagnosis that may become clear with further sampling. In many cases, however, definitive identification is not possible, and the final diagnosis has to be made of an indeterminate or simple cyst with no evidence of malignancy.

Mesothelial Proliferations

Mesothelial proliferation on the ovarian surface may arise as a response to pelvic inflammation but can also be seen in response to ovarian tumors and endometriosis [129–131]. In florid cases, there may be complex papillary or glandular mesothelial cell proliferations which may simulate neoplastic epithelial cells. Distinction can be made with immunohistochemistry for mesothelial markers such as calretinin, thrombomodulin, and D2/40 and epithelial markers such as BerEp4 and epithelial membrane antigen (EMA).

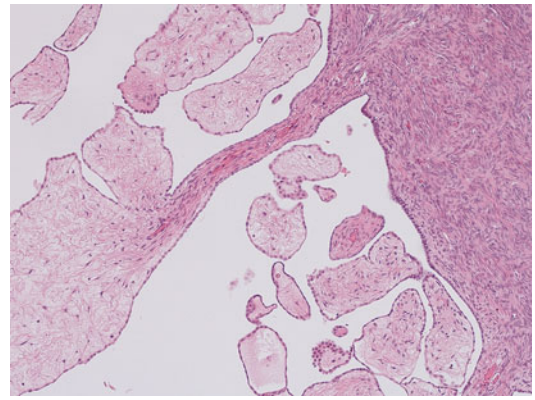

Fig. 2.18 Surface stromal proliferation. Incidental finding in an ovary removed at the time of hysterectomy. A size limit of 10 mm arbitrarily separates these from surface serous papillomas

Surface Stromal Proliferations

Nodular or papillary surface stromal projections are a common incidental finding on microscopic examination of the ovaries of postmenopausal and late reproductive age women. These are composed of ovarian stroma with varying hyalinization and a covering of a single layer of epithelial cells (Fig. 2.18). A size limit of 10 mm arbitrarily separates these proliferations, which are usually multiple, from surface serous papillomas.

Ovarian Remnant Syndrome

Ovarian remnant syndrome is defined as the presence of symptomatic ovarian tissue after bilateral salpingo-oophorectomy [132]. It is believed to result from unintentionally leaving ovarian tissue behind after a difficult operative procedure, often associated with adhesions such as in pelvic inflammatory disease or endometriosis [133]. Often the patient has had multiple prior operative

procedures. Clinically there may be a palpable mass or pelvic pain, as well as symptoms relating to the presence of functioning ovarian tissue. In a premenopausal patient with this syndrome, menopausal symptoms fail to occur, and the LH and FSH levels remain in the premenopausal range. Ovarian remnants can be removed at laparotomy or laparoscopy and are often attached by dense adhesions to residual pelvic structures. Residual ovarian tissue may be normal or may be enlarged by the presence of endometriosis or functional cysts. Very rarely a malignancy can develop in an ovarian remnant [134].

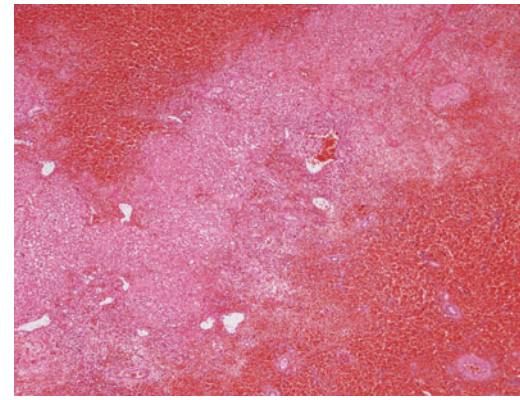

Fig. 2.19 Ovarian torsion. Hemorrhagic necrosis in a hyperstimulated ovary that had undergone torsion

Ovarian Hemorrhage

Ovarian hemorrhage is a common feature in follicular development but is usually minor and intrafollicular or perifollicular. Slight bleeding also occurs with follicular rupture at the time of ovulation, and bleeding also occurs in the vascularization stage of the corpus luteum [3]. Occasionally rupture of a corpus luteum or corpus luteum cyst may result in more severe hemorrhage and hemoperitoneum. This may occur at any time in the reproductive years but especially during pregnancy, and the risk is increased in association with anticoagulant treatment [135]. The right ovary is the source of hemorrhage in two thirds of patients.

Ovarian and Adnexal Torsion

Introduction: Ovarian torsion and hemorrhagic infarction is an uncommon but not a rare event, usually affecting women in reproductive years and is the fifth most common gynecological surgical emergency [136]. In adults, it usually occurs as a complication of an ovarian cyst or benign tumor such as a fibroma or mature cystic teratoma and occasionally a malignant tumor [137–139]. Rarely, particularly in children and young adults, normal ovaries may undergo torsion and infarction [140, 141]. There is also an increased risk of torsion of the normal ovary in pregnancy due to increased motility of the ovary in the first half of human pregnancy [142]. Torsion may also occur in ovarian hyperstimulation syndrome, including hyperreactio luteinalis [143, 144].

The fallopian tube and ovary may undergo torsion as a single unit rotating around the broad ligament, but less commonly the ovary undergoes torsion alone around the mesovarium. The right ovary is most commonly affected as movement of the left ovary is limited by the sigmoid colon [145].

Clinical Features: Clinically the presentation is with acute abdominal pain which may resemble acute appendicitis or with recurrent abdominal pain. Occasionally an adnexal mass is palpable. In children with torsion of a normal ovary, detorsion may be attempted to preserve ovarian function, but in adults excision of the ovary is usually necessary to exclude underlying neoplasia.

Histopathological Findings: Macroscopically the ovary is swollen and dark red. Microscopically there is hemorrhage, edema, and evidence of infarction with often frank necrosis (Fig. 2.19). Multiple blocks should be examined, especially of viable and solid areas at the periphery of the lesion, to determine any underlying cause such as a neoplasm. Complex cystic or papillary patterns raise suspicions of an underlying neoplasm. Necrotic tissue should be examined for the presence of shadows of neoplastic cells, and staining of reticulin fibers may help to identify underlying architecture when cellular detail is obscured.

Massive Ovarian Edema

Massive edema of the ovary is a rare condition affecting young women in their second and third decades and refers to unilateral or rarely bilateral tumorlike enlargement of both ovaries due to accumulation of edema fluid [146–149]. The median age affected is 21 years (range 6–33 years), and most present with abdominal pain and swelling, menstrual abnormalities, and features of androgen excess. The right ovary is affected in >75 % cases, but 10 % cases are bilateral. Partial or complete torsion of the ovary around the mesovarium is seen in 50 % of cases, and partial intermittent torsion that compromises venous and lymphatic drainage has been implicated in the pathogenesis. Management has often been by surgical removal to exclude the possibility of a neoplasm or complete torsion and ovarian ischemia, but conservative management may be possible and lead to resolution.

Macroscopically the ovaries are up to 35 cm diameter (mean 11 cm) with an opaque pearly outer surface, sometimes showing follicular cysts. The cut section is soft and gelatinous and exudes watery edema fluid. Microscopically the ovary shows diffuse edema of the medulla and cortex, although typically the peripheral cortex is spared and shows dense non-edematous collagenous tissue. The stroma is hypocellular and surrounds but does not displace native ovarian structures such as follicles. Clusters of luteinized cells are identified in around 40 % of cases and are thought to be the source of androgen production in patients who have virilization. Small numbers of mast cells, lymphocytes, and macrophages may be scattered within edematous areas. In a minority of cases, there are foci of fibromatous proliferation.

The differential diagnosis includes edematous fibroma and thecofibroma. Sclerosing stromal tumors compress the surrounding ovarian tissue and have a pseudolobular pattern. Metastatic carcinomas including Krukenberg tumors may show severe edema which can resemble massive ovarian edema, and the diagnostic cells may be sparsely distributed; a mucin stain or immunostaining for epithelial markers such as EMA or cytokeratin will establish the correct diagnosis. The relationship between massive edema and ovarian fibromatosis is not yet certain.

Fibromatosis

Ovarian fibromatosis is another cause of ovarian enlargement in young women and refers to overgrowth of collagen producing spindle cells that surround normal follicles. There is a strong clinical overlap with massive ovarian edema. Patients are young (mean 25 years; range 13–39 years), and patients often present with menstrual abnormalities and/or virilization and abdominal pain [148, 149]. There is evidence of torsion in some cases at the time of operation and transitional appearances between the two conditions have led to the suggestion that ovarian fibromatosis and massive ovarian edema represent ends of a spectrum of responses to a single pathogenetic mechanism. It is speculated that local tissue injury stimulates secretion of locally active growth factors that induce massive fibromatous proliferation and/or edema [3]. At operation, the process is bilateral in 20 % cases.

Macroscopically the ovaries are variable in size, sometimes only marginally enlarged, while other cases show ovaries 15 cm in diameter. The external surface may be lobulated or smooth, and the cut surface is typically firm and white or gray, sometimes with small cysts. Microscopically spindle cells surround follicular structures. The fibromatous proliferation is usually diffuse but may be confined to the ovarian cortex; cortical fibrosis is, however, common and this term should be restricted only to those cases where the fibrosis is particularly prominent. The appearances vary from moderate cellularity to a relatively acellular appearance. Luteinized cells may be scattered within cellular and edematous areas. In some cases, there are prominent proliferative features with dense cellularity and numerous normal mitoses, sometimes >20 mitoses per 10 high-power fields [3]. Apparent transition from this cellular form to less cellular collagenous forms has led to the suggestion that this may represent an "immature" form [3].

The differential diagnosis is with a fibroma, which lacks the entrapped normal follicular

structures. Stromal hyperthecosis is also seen in young women and is often bilateral, but it is not associated with acute presentation and does not lead to ovarian enlargement or show abundant collagen production. The more cellular form may be confused with luteinized thecomas which also occur in young women, but these are rare in women aged <20 years and are usually estrogenic and unilateral, while fibromatosis is often bilateral, inactive, or androgenic. Brenner tumors may enter the differential, but the typical epithelial nests should be easily distinguished.

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