THEMATIC REVIEW

SULFATION PATHWAYS

Contribution of intracrine oestrogens to the aetiology of endometriosis

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Abstract

Endometriosis is an incurable hormone-dependent inflammatory disease that causes chronic pelvic pain and infertility characterized by implantation and growth of endometrial tissue outside the uterine cavity. Symptoms have a major impact on the quality of life of patients resulting in socioeconomic, physical and psychological burdens. Although the immune system and environmental factors may play a role in the aetiology of endometriosis, oestrogen dependency is still considered a hallmark of the disorder. The impact of oestrogens such as oestrone and particularly, oestradiol, on the endometrium or endometriotic lesions may be mediated by steroids originating from ovarian steroidogenesis or local intra-tissue production (intracrinology) dependent upon the expression and activity of enzymes that regulate oestrogen biosynthesis and metabolism. Two key pathways have been implicated: while there is contradictory data on the participation of the aromatase enzyme (encoded by *CYP19A1*), there is increasing evidence that the steroid sulphatase pathway plays a role in both the aetiology and pathology of endometriosis. In this review, we consider the evidence related to the pathways leading to oestrogen accumulation in endometriotic lesions and how this might inform the development of new therapeutic strategies to treat endometriosis without causing the undesirable side effects of current regimes that suppress ovarian hormone production.

Key Words

- pain
- infertility
- steroid sulphatase
- oestrogen
- inflammation

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Introduction

Prevalence, characteristics and socioeconomic impact of endometriosis

Endometriosis is characterized by implantation and growth of endometrial tissue outside the uterine cavity (Agarwal *et al.* 2005). It is often associated with clinical symptoms that impair quality of life, including dysmenorrhoea, dyspareunia, acyclic pelvic pain, infertility and alterations of intestinal and urinary habits (Kyama *et al.* 2003, Bellelis

et al. 2014, Vercellini *et al.* 2014). Endometriosis lesions can form at different sites within the pelvis such as superficial peritoneal lesions, ovarian endometriomas (cysts) and may also be detected as deep-infiltrating lesions that can compromise other organs such as rectum and bladder (Chapron *et al.* 2006). The location of the lesion, its invasiveness and the presence and severity of adhesions in the peritoneal cavity were all taken into account by the American Society for Reproductive Medicine when

they proposed a characterization of the disorder into four stages (I-minimal, II-mild, III-moderate and IV-severe) (American Society for Reproductive Medicine 1997).

Endometriosis is a common disorder that is believed to affect 6–10% of women of reproductive age estimated to be ~176 million women worldwide (Bullett *et al.* 2010). An increased prevalence is commonly found in women with infertility, pelvic pain or both, with values ranging from 30 to 50% (Eskenazi & Warner 1997, Giudice & Kao 2004). Due to the severity of the symptoms experienced by some women with endometriosis, it has a high socioeconomic cost resulting in women being unable to work or care for their families and high associated health care costs in part because of the number of hospital admissions (Nnoaham *et al.* 2011, Fuldeore *et al.* 2015). For all these reasons, it has been argued that endometriosis should receive far greater attention and funding than it does currently (Signorile & Baldi 2010, Nnoaham *et al.* 2011, Culley *et al.* 2013, De Graaff *et al.* 2013, 2015, Vercellini *et al.* 2014, Fuldeore *et al.* 2015, Zubrzycka *et al.* 2015).

Genomics, genetics and lack of predictive biomarkers

Definitive diagnosis of endometriosis is based on the identification of lesions by visual inspection at the time of surgery. Importantly, there is poor correlation between extent of disease and severity of symptoms, which underlies our poor understanding of disease aetiology (Gopalakrishnan Radhika *et al.* 2016). Currently, there are no reliable, non-invasive biomarker tests which, in part, explains why diagnosis is often delayed for many years (Gupta *et al.* 2016, Nisenblat *et al.* 2016). Surgically confirmed disease occurs six- to nine-fold more commonly in first-degree relatives of affected women than in those of unaffected women (Kennedy 1999, Hompes & Mijatovic 2007), which has led to the classification of endometriosis as a polygenic, heritable disease and prompted the search for genetic biomarkers. A recent meta-analysis of 11 genome-wide association case-control data sets, involving 17,045 endometriosis cases identified five new genetic loci (SNPs) significantly associated with endometriosis risk implicating genes involved in sex steroid hormone pathways that included *FN1*, *CCDC170*, *ESR1*, *SYNE1* and *FSHB* genes (Sapkota *et al.* 2017). In addition, genomic analysis of eutopic endometrium has reported differential expression of key genes between samples from women with endometriosis and those without (Aghajanova *et al.* 2009, Zelenko *et al.* 2012) that are associated with alterations in functional activities (Nikoo *et al.* 2014).

These findings offer potential for development of new diagnostic approaches based on genetic or tissue profiling (Tamareis *et al.* 2014) with the former prompting the formation of large multinational consortia to test findings using larger datasets (Montgomery *et al.* 2008).

Current therapies

Current treatments for endometriosis-associated pelvic pain and/or infertility include both surgical and medical approaches. Due to the high costs and risks associated with surgery, it is frequently considered as a second choice with priority given to medical therapy for mild/moderate disease. For severe disease, particularly, that involves obstructive urinary/intestinal lesions or large endometrioma, surgery is the first choice (Halpern *et al.* 2015). Surgical removal of lesions can offer some relief from pain and may improve fertility; however, recurrence of symptoms is reported in up to 75% of women within 5 years of surgery (Guo 2009). Although the cause(s) of endometriosis remain incompletely understood, there is intense research activity involving observations on primary samples and fluids (blood, peritoneal), *in vitro* studies using cells isolated from patients and controls, as well as testing in a range of preclinical animal models (see recent review by Greaves *et al.* 2017) all directed at gaining knowledge that might be translated into more effective ways to prevent recurrence or treat symptoms.

It is widely accepted that inflammatory processes can contribute to the development of endometriosis and associated pain symptoms (Králíčková & Vetvicka 2015). However, currently, it is the hormone (oestrogen) dependence of the disease that has been most effectively targeted by medical therapy. The first-line treatments of hormonal therapies work by suppressing ovarian function: this includes use of GnRH agonists and birth control pills, whereas others utilise inhibitors of the aromatase enzyme, which is essential for biosynthesis of oestrogens by ovarian follicles (Lindsay *et al.* 2015, Vercellini *et al.* 2016). Some reports suggest these treatments may result in pain reduction up to 80% of endometriosis patients, especially when a combination of drugs is used (Platteuw & D'Hooghe 2014, Zhao *et al.* 2015). However, gonadotropin-releasing hormone analogue or aromatase inhibitor (AI) therapies are associated with negative side effects that mimic a premature menopause (including hot flashes symptoms) while birth control pills are not ideal for women wanting to get pregnant. Also, a proportion of patients either fail to respond or relapse after relatively short period of time. In the search for new therapies, steroid

sulphatase (STS) inhibitors originally developed as a new drug for oestrogen-dependent breast cancers are being considered (Purohit *et al.* 2008). The suggestion that STS inhibitors could be repurposed for treating endometriosis has been supported by reports using murine models of endometriosis where a 40% reduction in lesions size was reported following oral treatment with oestradiol-3-O-sulfamate, a readily absorbed and transformed STS inhibitor (Colette *et al.* 2011). In the following review, we consider the evidence that endometriosis is an oestrogen-dependent disorder, that local oestrogens generated *in situ* are important regulators of disease and how this might inform new therapies avoiding undesirable side effects.

Endometriosis: an oestrogen-dependent disorder

Sources of endometrial-acting oestrogens

During a woman's reproductive years, the primary site of synthesis of the bioactive oestrogens, oestrone (E1) and oestradiol (E2) are the ovaries, particularly the ovarian follicles. Oestrogen biosynthesis by ovarian follicular cell types has been extensively reviewed (Lessey *et al.* 1989, Huhtinen *et al.* 2012a). In brief, it begins with the transport of cellular cholesterol from the cytosol to mitochondria matrix by steroidogenic acute regulatory protein (STAR). Inside the mitochondria, cholesterol is converted into pregnenolone by cholesterol side-chain cleavage enzyme (P450_{scc}, encoded by CYP11A1). Pregnenolone can then be transformed into progesterone by 3 β -hydroxysteroid dehydrogenase type 2 (HSD3B2) (Attar *et al.* 2009). Pregnenolone can also be converted into 17 β -hydroxypregnenolone, DHEA and then androstenedione by steroid 17 α -monooxygenase (17, 20-lyase, P450_{c17}, encoded by CYP17A1), which in turn can be reduced to testosterone primarily by 17 β -hydroxysteroid dehydrogenase 3 (HSD17B3), mainly expressed in testis, and AKR1C3 which is expressed in endometrium and endometriosis (Catalano *et al.* 2011, Sinreih *et al.* 2015). Androstenedione and testosterone are substrates of the aromatase complex (P450_{arom}, encoded by CYP19A1), which are converted to E1 and E2, respectively. Finally, HSD17B1 can convert E1 into E2, considered to be the more potent bioactive form of oestrogen: both E1 and E2 can bind and activate oestrogen receptors.

There is also evidence that oestrogens can be synthesized in extra-ovarian sites including the endometrium, endometriosis lesions (discussed below) and adipose tissue. According to the concept

of intracrinology (Labrie *et al.* 2000), extra-ovarian tissues that express the enzymes that regulate oestrogen biosynthesis have the capacity to utilize blood borne precursors including DHEA and the sulphated oestrogens (E1S and E2S). One potential extra-ovarian site for E2 biosynthesis is adipose tissue (Kim *et al.* 2014). Adipose cells express oestrogen-synthesizing enzymes (Nelson & Bulun 2001), and *in vitro* production of oestrogens has been described (Ghosh *et al.* 2013). It remains unknown whether the oestrogen produced by adipose tissues has any impact on the amount of circulating E1/E2 or if this has an impact on the endometrium or endometriosis lesion development. However, as women with endometriosis have a significantly lower body mass index than women without disease (Vitonis *et al.* 2010), it is less likely that adipose-derived oestrogens have a prominent role in endometriosis development.

Notably, endometrial tissue homogenates are reported to contain two to five times greater concentrations of E2 compared to the serum levels (Huhtinen *et al.* 2012b) consistent with a potential role for intracrine synthesis. One possible source of E2 is the reduction of E1 present in the blood bathing the tissue to E2 by action of the reductive enzyme HSD17B type 1 that has been consistently detected in the endometrium and differs between ectopic and eutopic tissue (Huhtinen *et al.* 2012b, Delvoux *et al.* 2014). Although aromatase expression has not been detected in stromal cells isolated from healthy endometrium during the proliferative phase, it is reported to be upregulated in response to a decidualization stimulus (progesterone and cAMP), suggesting that this enzyme may play a role in intracrine production of E2 required for regulation of immune and other cells in preparation for embryo implantation (Gibson *et al.* 2013, 2015, 2016). Clearly, further studies are needed to fully understand the local mechanisms of oestrogen biosynthesis and metabolism in the healthy endometrium, taking into account reports of an impaired response to progesterone in women with endometriosis (termed 'progesterone resistance', Burney *et al.* 2007).

Expression of oestrogen receptors and impact of oestrogen on normal endometrium

In humans, two isoforms of oestrogen receptor have been identified: ER α (NR3A1) and ER β (NR3A2). These are encoded by two separate genes, *ESR1* and *ESR2*, respectively, located on the human chromosomes 6q25.1 (*ESR1*) and 14q23.3 (*ESR2*) (Nilsson *et al.* 2001). The messenger RNAs for both receptors are present in the human endometrium,

and detailed immunohistochemical analysis has revealed that expression of the two receptors are distinct with respect to cell type with changes in the epithelial cells being regulated according to stage of the cycle (Critchley *et al.* 2001). Studies in mouse models have identified a key role for ER α in both stromal–epithelial interactions and the regulation of epithelial cell proliferation (Hewitt *et al.* 2017). Notably, ER β but not ER α is present in the vascular endothelium of the human and non-human primate endometrium and appears to regulate the E2 responsiveness of these cells consistent with oestrogen regulation of angiogenesis (Critchley *et al.* 2001, Greaves *et al.* 2013). The impact of E2 on diverse immune cell populations may also be regulated by ER β as the receptor has been detected in the nuclei of uterine natural killer (uNK) (Henderson *et al.* 2003) and mast cells (De Leo *et al.* 2017). Notably, recent studies have demonstrated that uNK cells treated with E2 release the chemokine CCL2, which promotes endometrial endothelial cells to form angiogenesis networks (Gibson *et al.* 2015). This will, in turn, provide a potential mechanism by which local E2 might have an impact on cell types that play a key role in establishment of endometriosis lesions.

Detection of steroids in endometrium and endometriosis lesions

Traditionally, oestrogens have been measured using either gas chromatography/mass spectrometry or immunoassay. The development of highly sensitive liquid chromatography coupled with tandem mass spectrometry (LC-MS-MS) as a technique for steroid detection offered an approach for more precise, accurate detection of E2 (Harwood & Handelsman 2009). Using LC-MS-MS, it has been possible to measure E2 and E1 in endometrial tissue homogenates demonstrating that they vary according to menstrual cycle phase and that they do not parallel serum levels (Huhtinen *et al.* 2012b). In endometriosis lesions, E2 was the most abundant oestrogen and concentrations were independent of cycle phase in peritoneal and deep-infiltrating lesions (Huhtinen *et al.* 2012b). Notably, alterations in expression of many of the enzymes involved in biosynthesis and metabolism of oestrogens in endometriosis and endometrial cancer has been reviewed previously (Rižner 2009, 2013, Huhtinen *et al.* 2012a) with parallels to reports of local oestrogen biosynthesis in endometrial cancer (as reviewed by Rižner *et al.* 2017) with a pro-oestrogenic environment reported to drive cell proliferation in the latter.

Expression of oestrogen receptors in endometriosis lesions

Differences in expression of ESR1 and ESR2 in endometriotic tissue have been reported by several groups (reviewed by Rižner 2009, Huhtinen *et al.* 2012a). The Bulun group has investigated the expression of oestrogen receptors in endometriosis lesions (reviewed in Bulun *et al.* 2012), reporting overexpression of ER β and identifying changes in promoter methylation as a possible mechanism (Xue *et al.* 2007). Immunohistochemical analysis has localized ER β to both immune cells and nerves in lesions recovered from women and animal models (Greaves *et al.* 2015). Remarkably, as shown in studies using *in vitro* models, E2 can have an impact on nerves, vascular cells and immune cells, and it has been suggested they could be regulated via ER β . It has also been postulated that E2 may have an impact on neuroangiogenesis (Greaves *et al.* 2014) and contribute to pain mechanisms (Liang & Yao 2016). Following the development of ER β -selective agonists and antagonists (reviewed in Burris *et al.* 2013), these observations that ER β was overexpressed in endometriosis lesions prompted investigations in preclinical models to see if they might offer a novel therapeutic option. Although some results from preclinical tests appeared promising (reviewed by Harris 2007) to date, there has been limited transparency about the results of clinical trials (Guo *et al.* 2009) and searches do not suggest they are still in active development for treatment of this condition.

Local (intracrine) biosynthesis of oestrogens in endometriosis

Until recently, it has been widely accepted that the pathway most likely to influence local concentrations of E1/E2 in endometriotic lesions is the one that culminates in transformation of androgens into oestrogens by the aromatase enzyme complex (P450arom). However, a second pathway that depends on the ability of STS to convert conjugated steroids found at high concentration in blood such as sulphated oestrogens oestradiol sulphate (E2S) and oestrone sulphate (E1S) into bioactive E2 or E1, respectively, is also likely to be playing a role. In endometriotic lesions, oestrogens can be formed by the following three main pathways: (i) *de novo* from cholesterol; (ii) from androstenedione or testosterone via the aromatase pathway or (iii) from E1S via the sulphatase pathway. Evidence for all these pathways operating in the context of endometriosis is reviewed below.

Pathways utilizing cholesterol to generate androgens or progestins

Table 1 summarizes articles that study the main enzymes that utilize cholesterol to generate androgens or progestins.

Steroidogenic acute regulatory protein

Cholesterol is a ubiquitous steroid precursor, and STAR regulates the transport of cholesterol from the outer membrane to the inner membrane of mitochondria where it can be metabolized into pregnenolone by P450scc (Soffientini & Graham 2016). STAR mRNA expression was found to be higher in ectopic endometrium compared to eutopic and control endometrium (Tsai *et al.* 2001, Attar *et al.* 2009, Huhtinen *et al.* 2014). Moreover, between eutopic and control endometrium, STAR was described as more pronounced in eutopic endometrium of endometriosis patients (Tsai *et al.* 2001, Sun *et al.* 2003), showing a correlation with the severity of the disease (Tian *et al.* 2009). Utsunomiya *et al.* (2008) went further, suggesting that alterations in the amount of the transcription factor steroidogenic factor 1 (SF-1), which promotes expression of both STAR and P450arom, was regulated by higher expression of stimulatory factor type 2 (USF2) that was uniquely expressed in ectopic stromal endometrium cells. Thus, dysregulation in stromal endometriotic cells may be causing enhanced expression of SF-1, which in turn

upregulates STAR mRNA expression (Shen *et al.* 2013). Prostaglandin E2 (PGE2), present in high concentrations in inflammatory diseases such as endometriosis, also stimulates STAR expression in human endometriotic stromal cells (Tsai *et al.* 2001, Hsu *et al.* 2008, Attar *et al.* 2009), which could also increase the concentration of mitochondrial cholesterol and favour increased oestrogen biosynthesis. Conversely, a lack of difference in STAR expression between eutopic endometrium from women with vs without endometriosis was reported in one study (Aghajanova *et al.* 2009) suggesting further investigations are required.

Cholesterol side chain cleavage (CYP11A1)

The cholesterol side chain cleavage enzyme (encoded by *CYP11A1*, also referred to as CYP450scc) that is responsible for converting cholesterol into pregnenolone is located exclusively within the inner mitochondria membrane (Van 2013). An *in vivo* experiment by Attar *et al.* described higher CYP450scc mRNA levels in ectopic lesions compared with control endometrium (Attar *et al.* 2009). Conversely, in other studies, no differences in *CYP11A1* mRNA expression between eutopic control endometrium and ectopic endometrium were recorded (Tsai *et al.* 2001, Aghajanova *et al.* 2009). Interestingly, treatment of endometrial epithelial and stromal cell cultures from

Table 1 mRNA expression of enzymes from pathways utilizing cholesterol to generate androgens or progestagens.

Enzyme	Patient number	Sample number	Differential expression	Reference
STAR	E=29; C=13	EE=7; CE=6	EE=CE	Aghajanova <i>et al.</i> (2009) Attar <i>et al.</i> (2009) Shen <i>et al.</i> (2013)
	E=30; C=16	EL=13; OE=17; CE=16	↑ EL/CE	
	E=23; C=15	EL=23; EE=23; CE=15	↑ EL; EE/CE ↑ EL/EE	
	E=30; C=25	EL=30; CE=25	↑ EL/CE	Tian <i>et al.</i> (2009)
	E=35; C=15	EL=25; OE=10; ADM=4; CEL=10; CE=1	↑ EL; OE/ADM; CL; CE	Tsai <i>et al.</i> (2001)
CYP11A1	E=29; C=13	EE=7; CE=6	EE=CE	Aghajanova <i>et al.</i> (2009) Attar <i>et al.</i> (2009) Fouquet <i>et al.</i> (2016)
	E=30; C=16	EL=13; OE=17; CE=16	↑ EL/CE	
	E=38; C=31	EL=16; EE=16; CE=31	↑ EL; EE/CE	
	E=60; C=16	EL=23; OE=18; EE=18; CE=16	↑ OE/CE	Huhtinen <i>et al.</i> (2014)
	E=35; C=15	EL=25; OE=10; ADM=4; CL=10; CE=1	↑ EL; OE=ADM; CL; CE	Tsai <i>et al.</i> (2001)
HSD3B2	E=29; C=13	EE=7; CE=6	EE=CE	Aghajanova <i>et al.</i> (2009) Attar <i>et al.</i> (2009) Huhtinen <i>et al.</i> (2014) Tsai <i>et al.</i> (2001)
	E=30; C=16	EL=13; OE=17; CE=16	↑ EL/CE	
	E=60; C=16	EL=23; OE=18; EE=18; CE=16	↑ EL; OE/CE	
	E=35; C=15	EL=25; OE=10; ADM=4; CL=10; CE=1	↑ EL; OE=ADM; CL; CE	
P450c17	E=30; C=16	EL=13; OE=17; CE=16	↑ EL/CE	Attar <i>et al.</i> (2009)
	E=38; C=31	EL=16; EE=16; CE=31	↑ EL; EE/CE	Fouquet <i>et al.</i> (2016)
	E=60; C=16	EL=23; OE=18; EE=18; CE=16	↑ OE/CE	Huhtinen <i>et al.</i> (2014)

ADM, adenomyosis myometrium; C, control patients – control patients are considered all women without endometriosis; CE, control endometrium; CEL, control endometrium from leiomyoma patients; E, endometriosis patients; EE, eutopic endometrium from endometriosis; EL, endometriosis lesion-extraovarian; OE, ovarian endometriosis.

women with and without endometriosis with PGE2 promoted increased levels of *CYP11A1* gene expression (Attar *et al.* 2009, Fouquet *et al.* 2016), indicating that inflammatory mediators may also influence the expression of this steroidogenic enzyme.

HSD3B2

The steroidogenic enzyme HSD3B catalyzes the conversion of pregnenolone into progesterone, DHEA into androstenedione and also 17-hydroxypregnenolone into 17-hydroxyprogesterone. 3 β -HSD (isoform not specified) are expressed in the ovary (Simard *et al.* 2005) and endometrium (Casey *et al.* 1994). The published studies evaluated difference in HSD3B2 expression in the endometriosis patients, Tsai *et al.* and Aghajanova *et al.* observed no difference in amount of HSD3B2 expression between normal and ectopic endometrium (Tsai *et al.* 2001, Aghajanova *et al.* 2009). In contrast, other studies, higher HSD3B2 mRNA concentrations and enzyme activity were detected in ectopic vs eutopic endometrium (Attar *et al.* 2009, Huhtinen *et al.* 2014), suggesting a greater intra-lesion synthesis of steroidogenesis precursors. To further investigate the regulation of HSD3B2 in endometriosis patients, Urata and colleagues designed an experiment to test the effect of PGE2 and interleukin 4 (IL-4), a cytokine known to be present in high levels in women with endometriosis, on stromal cells from endometrioma, showing that both factors enhanced HSD3B2 mRNA expression in a dose-dependent manner (Urata *et al.* 2013). Similar findings were described by Attar *et al.* (2009). Nevertheless, the treatment with IL-4 or PGE2 did not produce an effect on HSD3B2 mRNA expression in stromal cells from eutopic endometrium (Urata *et al.* 2013).

CYP17A1

Steroid 17 α -monooxygenase catalyzes the conversion of progestins to androstenedione by firstly converting progesterone and pregnenolone into 17-hydroxyprogesterone and 17-hydroxypregnenolone, respectively. Afterwards, 17-hydroxyprogesterone is further metabolized by P450c17 into androstenedione. Alternatively, 17-hydroxypregnenolone can either be converted into DHEA or 17-hydroxyprogesterone by P450c17 and HSD3B2, respectively. HSD3B2 catalyzes the conversion of DHEA into androstenedione (Simard *et al.* 2005, Tsuchiya *et al.* 2005a). Increasing the expression of P450c17 in HEK 293 cells enhances the formation of DHEA and diminishes 17-hydroxypregnenolone showing

the importance of this enzyme in complex steroidogenesis pathways (Soucy & Van 2000). In endometriosis, P450c17 mRNA expression was found to be higher in ectopic lesions (ovarian endometrioma and/or peritoneal tissue) compared with control endometrium (Borghese *et al.* 2008, Attar *et al.* 2009, Huhtinen *et al.* 2014). The same higher expression was observed in epithelial and stromal endometriotic cells (Attar *et al.* 2009). As with CYP11A1 and HSD3B2 enzymes, the expression of P450c17 in stromal endometriotic cell cultures was also enhanced by treatment with PGE2 highlighting the potential for pro-inflammatory factors to have an impact on multiple enzymes within the steroidogenic pathways to regulate steroid synthesis in endometriosis (Tsai *et al.* 2001, Attar *et al.* 2009). Moreover, P450c17 expression in epithelial endometriotic cells was also enhanced by human chorionic gonadotropin and insulin like-3, both factors known to be involved in cell growth, differentiation, invasion and vascularization, all pathophysiological mechanism implicated in the development of the disease (Fouquet *et al.* 2016). On the contrary, others have reported no difference in expression of P450c17 between eutopic endometrium from women with and without endometriosis (Aghajanova *et al.* 2009). The *CYP17* gene, located on chromosome 10q24.3, has been intensively studied to find disease-associated polymorphisms (Soucy & Van 2000); some have been correlated with variations in steroid hormone levels, menstrual factors and risk of endometrial and breast cancers (Devore & Scott 2012). However, although several studies have tried to relate polymorphisms in *CYP17* with susceptibility to endometriosis (Supplementary Table 1, see section on supplementary data given at the end of this article), there is as yet no clear evidence for a correlation.

Pathways utilizing androgens to generate oestrogens

Table 2 summarizes articles that study the main enzymes, which utilize androgens to generate oestrogens.

AKR1C3

Aldo-keto reductase family 1 member C3 (AKR1C3; also known as 17 β hydroxysteroid dehydrogenase type 5) is a steroidogenic enzyme with diverse substrate specificities and activities. AKR1C3 may contribute to a pro-oestrogenic state in endometriosis as studies investigating the enzyme kinetics of the recombinant human protein suggest AKR1C3 can promote (i) direct reduction of E1

Table 2 mRNA expression of enzymes from pathways utilizing androgens to generate oestrogens.

Enzyme	Patient number	Sample number	Differential expression	Reference
AKR1C3	E=24; C=10	OE=24; CE=10	↑ OE/CE	Šmuc <i>et al.</i> (2009)
	E=31; C=37	OE=31; CE=28; CEM=9	↑ OE/CE; CEM	Hevir <i>et al.</i> (2011)
	E=60; C=16	EL=4; OE=4; EE=4; CE=4	EL=OE=EE=CE	Huhtinen <i>et al.</i> (2012b)***
	E=45; C=29	EL=21; EE=45; CE=29	↑ EL/CE* EL=EE	Rakhila <i>et al.</i> (2013)
CYP19	E=14; C=48	EL=14; EE=14; CE=48	CE [^]	Dassen <i>et al.</i> (2007)
	E=30; C=16	EL=13; OE=17; CE=16	↑ EL/#CE	Attar <i>et al.</i> (2009)
	E=29; C=13	EE=7; CE=6	↑ EE/CE	Aghajanova <i>et al.</i> (2009)
	E=14; C=15	EL=14; EE=12; CE=8; CFE=7	↑ EE/#CE; CFE	Bukulmez <i>et al.</i> (2008b)
			↑ EL/EE	
	E=38; C=31	EL=16; EE=16; CE=31	↑ EL and EE/#CE	Fouquet <i>et al.</i> (2016)
	E=60; C=16	EL=23; OE=18; EE=18; CE=15	↑ OE/#CE	Huhtinen <i>et al.</i> (2012b)***
	E=10; C=20	EL=10; EE=10; ADM=10; CCE=10	↑ EL; EE; ADM/CCE	Kitawaki <i>et al.</i> (1997)
	E=42; C=21	EE=42; CCE=21	↑ EE/#CCE	Kitawaki <i>et al.</i> (1999)
	E=15; C=19	EL=15; EE=15; CE=19	↑ EL/EE; CE	Morsch <i>et al.</i> (2009)
	E=17; C=7	EL=17; EE=11; CE=7; ENP=7	↑ EL; EE/#CE; ENP	Noble <i>et al.</i> (1996b)
	E=23; C=15	EL=23; EE=23; CE=15	↑ EL; EE/#CE	Shen <i>et al.</i> (2013)
			↑ EL/EE	
	E=16; C=9	OCE=16; COC=9	↑ OE/#COC	Šmuc <i>et al.</i> (2007)
	E=24; C=10	OE=24; CE=10	↑ OE/CE	Šmuc <i>et al.</i> (2009)

#Absence of mRNA expression; ^mRNA expression near detection limit; *only when comparing patients in the proliferative phase; ***when comparing patients in the proliferative vs secretory phase. It was considered significant all mRNA expression with $P < 0.005$.

ADM, adenomyosis myometrium; C, control patients – control patients are considered all women without endometriosis; CCE, cervical carcinoma endometrium; CE, control endometrium; CEM, control endometrium with myoma; CFE, control with fibrosis endometrium; COC, control ovarian cyst; E, endometriosis patients; EE, eutopic endometrium from endometriosis women; EL, endometriosis lesion-extraovarian; ENP, endometriosis normal peritoneum; OCE, ovarian endometriotic cyst from patients with endometriosis; OE, ovarian endometriomas.

to the more potent E2 and (ii) reduction of progesterone to less potent metabolite 20 α -hydroxyprogesterone (Penning *et al.* 2000). In hormone-dependent cancers, AKR1C3 is reported to promote activation of oestrogens by catalysing the reduction of E1 to E2, which promotes proliferation of MCF7 breast cancer cells (Penning & Byrns 2009). In addition, AKR1C3 catalyses reduction of androstenedione to testosterone, which may impact on androgen–oestrogen balance in the endometrium.

AKR1C3 has been detected in the human endometrium with peak expression reported in the early secretory phase of the menstrual cycle (Catalano *et al.* 2011). Expression of AKR1C3 mRNA measured by qPCR in endometriosis has been reported in tissue from peritoneal, ovarian and deep-infiltrating endometriosis, but no significant changes in expression were reported across menstrual cycle phase or between different tissue types (Huhtinen *et al.* 2012b). Hevir *et al.* reported AKR1C3 mRNA is modestly increased in ovarian endometriomas compared to normal endometrium (Hevir *et al.* 2011) while the same group subsequently found that expression of AKR1C3 protein was unchanged between endometrioma and control endometrium (Sinreih *et al.* 2015). Recent reports suggest AKR1C3 is increased in primary ectopic endometrial cells from ovarian endometriomas compared to cells isolated

from control endometria, although the cell types isolated from these tissues were not stated in the study (Kim *et al.* 2017). Immunohistochemistry analysis of AKR1C3 in endometrioma tissues demonstrated expression mainly detected in epithelial and to a lesser extent in stromal cells (Hevir *et al.* 2011). Analysis of cell lines derived from peritoneal endometriosis tissues suggest AKR1C3 mRNA is increased in peritoneal endometriosis stromal cell lines (22-B) compared to control stromal cell lines (HIESC) (Sinreih *et al.* 2015). In contrast, AKR1C3 mRNA expression was decreased in 12-Z epithelial cells derived from peritoneal endometriosis compared to control HIEEC epithelial cell line (Sinreih *et al.* 2015). Rakhila *et al.* investigated AKR1C3 mRNA expression in women with stage I–II endometriosis (American Fertility Society classification system (Practice & Medicine 2012) and reported increased AKR1C3 in ectopic endometrium compared to control endometrium (Rakhila *et al.* 2013). Notably, when samples were stratified according to menstrual cycle stage, a significant increase in AKR1C3 was only detected in samples from the proliferative phase of the cycle highlighting the complexity of interpreting AKR1C3 expression studies (Rakhila *et al.* 2013). Taken together, these studies suggest endometrial AKR1C3 may contribute to an altered steroid environment within

endometriosis lesions but further studies are required to establish if this affects growth/persistence of endometriosis lesions. Notably, AKR1C3 also catalyses reduction of isoprenyl aldehydes as well as retinaldehydes with high catalytic efficiency as compared to other substrates (Endo *et al.* 2011, Ruiz *et al.* 2011). In addition, AKR1C3 can function as a prostaglandin F₂ α (PGF₂ α) synthase and PGF₂ α concentrations are elevated in the peritoneal fluid from endometriosis patients compared to healthy women (Sinreih *et al.* 2015). AKR1C3 may therefore have diverse effects and influence multiple signalling pathways in endometriosis.

Aromatase (CYP19)

Aromatase (P450arom), encoded by *CYP19A1*, is a member of the cytochrome P450 family. This enzyme plays a key role in oestrogen biosynthesis by catalysing the aromatization of the androgens, androstenedione and testosterone into E₂ and E₁, respectively. The *CYP19A1* gene is located in chromosome 15q21.2 and the association of polymorphism and endometriosis risk in different ethnicities has been explored; however, the results are inconsistent and inconclusive, even within the same population (Supplementary Table 2) (Yi *et al.* 2016). There have also been differing results reported related to the presence or absence of P450arom in endometrium and ectopic lesions with reports of atypical expression in patients with endometriosis (Bulun *et al.* 2004, Ferrero *et al.* 2014, Blakemore & Naftolin 2016). Several studies report that protein and mRNA expression of P450arom can be detected in ectopic and/or eutopic endometrium of endometriosis patients, but not in normal endometrium (Noble *et al.* 1996a, Kitawaki *et al.* 1997, 1999, Tsai *et al.* 2001, Dassen *et al.* 2007, Hudelist *et al.* 2007, Smuc *et al.* 2007, Bukulmez *et al.* 2008a, Attar *et al.* 2009, Šmuc *et al.* 2009, Morsch *et al.* 2009, Huhtinen *et al.* 2012b, 2014, Shen *et al.* 2013, Suganuma *et al.* 2014, Fouquet *et al.* 2016) although this is disputed by others who failed to detect expression in either ectopic or eutopic endometrial tissue (Colette *et al.* 2009, Delvoux *et al.* 2009, 2014), others record expression in normal endometrium (Tseng 1984, Neulcn *et al.* 1987, Huang *et al.* 1989, Castro *et al.* 2010) and in endometrium from women with and without endometriosis (Aghajanova *et al.* 2009). Variations in the location of P450arom have also been recorded with detection in epithelial cells (Kitawaki *et al.* 1997, Bukulmez *et al.* 2008a, Castro *et al.* 2010), but mostly in stromal cells (Noble *et al.* 1996a, Zeitoun *et al.* 1999, Suganuma *et al.* 2014) (Supplementary Tables 3

and 4). Some of the variations in the reported patterns of expression may relate to use of different antibodies, recovery of eutopic endometrium at different stages of the cycle, the type of lesion or the status of the inflammatory microenvironment as discussed below.

A number of factors that are altered in endometriosis patients can induce the expression of P450arom. For instance, the observed increase in concentrations of androstenedione (Huhtinen *et al.* 2014) may induce P450arom expression in human endometrial stromal cells and the human endometrial surface epithelial (HES) cell line, as has been previously described (Bukulmez *et al.* 2008b). Inflammatory cells or inflammatory mediators may also have an impact. For example, P450arom protein and mRNA were enhanced by macrophage activity in endometrial stromal and endometrial cells, and macrophage inhibition significantly reduced P450arom expression (Veillat *et al.* 2012). In different experiments, treatments of stromal cells derived from ovarian endometrioma, with PGE-2 or IL-(1, 2, 4, 6, 11, 15) stimulated expression of P450arom in a time- and dose-dependent manner (Noble *et al.* 1997, Urata *et al.* 2013, Zeng *et al.* 2015). Interestingly, in these experiments, eutopic endometrial cells showed low levels of P450arom mRNA expression and not upregulated by PGE-2 or ILs, suggesting there may be different responses in eutopic vs ectopic tissues.

Accordingly, in face of these conflicting results, controversy still exists with regard to the association between P450arom expression and clinical symptoms of endometriosis. Higher CYP17A1 GG genotype was linked to infertility although there were no differences between patients with endometriosis and patients without endometriosis (Szczepańska *et al.* 2013). In a study on 62 women with endometriosis, positive immunohistochemical expression for aromatase was detected in the endometriotic tissues from 38 patients (61.3%): these patients were more likely to have ovarian disease and moderate-to-severe chronic pelvic pain (Acién *et al.* 2007).

Pathways utilizing sulphated steroids

Although the synthesis of E₁ and E₂ from the sulphated oestrogens (E₁S and E₂S, respectively) is usually considered less important than the aromatase pathway in the ovary, for peripheral tissues including the endometrium it seems to be an important alternative pathway that leads to increased bioavailability of local active oestrogens (reviewed by Rižner 2016). Thus, due

to the possible impact that sulphonation pathway could have in oestrogen-dependent diseases, research groups around the world investigated the possible involvement of sulphated steroids and their respective enzymes in endometriosis (Purohit *et al.* 2008, Delvoux *et al.* 2014). Table 3 summarizes articles that study the main enzymes that utilize sulphated steroids including two forms of sulphotransferases (SULTs) not discussed below.

Steroid sulphatase

STS is the enzyme responsible for the hydrolysis of dehydroepiandrosterone sulphate, E1S and E2S into their unconjugated forms, DHEA, E1 and E2, respectively (Reed *et al.* 2005). Although the mRNA expression and activity of STS is increased in malignant endometrial tissues compared with nonmalignant tissues according to the majority of studies (Hevir *et al.* 2011, 2013), data on STS mRNA and protein expression have only recently emerged from studies on endometriosis. The expression of STS in endometriosis has been reviewed by Rižner 2009, where comparisons of STS expression in eutopic and ectopic tissue from the same patients as well as comparison of expression in ectopic tissue vs eutopic tissue of control

patients were evidenced. Overall, most studies agree that there is a differential STS mRNA expression between eutopic and ectopic endometrium, in spite of conflicting results in regards of STS expression among endometriotic lesions. Data from our group show higher STS mRNA expression in deep-infiltrating and superficial lesions when compared to eutopic and normal endometrium, with neither differences between ectopic lesions, nor between eutopic and normal endometrium (Piccinato *et al.* 2016a). Some authors have reported higher STS mRNA expression in ovarian lesions when compared to endometrium from patients with myoma (Smuc *et al.* 2007, Šmuc *et al.* 2009), while others have not been able to detect differences between lesions, compared to the eutopic endometrium (Colette *et al.* 2013, Huhtinen *et al.* 2014). Similarly, in deep-infiltrating lesions, both an unaltered expression pattern (Dassen *et al.* 2007) and greater expression of STS mRNA expression relative to that in ovarian lesions have been described (Colette *et al.* 2013).

Only a few researchers have attempted to quantify STS protein expression. Collette *et al.* reported no differences in protein levels between tissues from endometriosis patients and controls (Colette *et al.* 2013). In contrast to that, Dassen *et al.* reported increased expression levels of

Table 3 mRNA expression of enzymes from pathways utilizing sulphated steroids.

Enzyme	Patient number	Sample number	Differential expression	Reference
STS	E=60; C=16	EL=23; OE=18; EE=18; CE=16	OE=CE EE=CE EL=CE	Huhtinen <i>et al.</i> (2014)
	E=62; C=16	EL=34; EE=24; CE=25	↑ EL/EE; CE	Piccinato <i>et al.</i> (2016a)
	E=16; C=9	OCE=16; COC=9	↑ OE/COC	Smuc <i>et al.</i> (2007)
HSD17B1	E=24; C=10	OE=24; CE=10	↑ OE/CE	Šmuc <i>et al.</i> (2009)
	E=29; C=13	EE=7; CE=6	EE=CE	Aghajanova <i>et al.</i> (2009)
	E=29	EL=23; OE=6; EE=29	↑ EL; OE/EE	Delvoux <i>et al.</i> (2014)
	E=60; C=16	EL=23; OE=18; EE=18; CE=15	↑ OE/CE	Huhtinen <i>et al.</i> (2012b)***
	E=16; C=9	OCE=16; COC=9	↑ OE/COC	Smuc <i>et al.</i> (2007)
SULT1A1	E=24; C=10	OE=24; CE=10	↑ OE/CE	Šmuc <i>et al.</i> (2009)
	E=79; C=41	EL=30; OE=15; EE=33; CE=15	EL=OE=EE=CE	Colette <i>et al.</i> (2013)
	E=31; C=29	OE=31; CE=29	OE=CE	Hevir <i>et al.</i> (2013)
SULT1E1	E=24; C=10	OE=24; CE=10	OE=CE	Šmuc <i>et al.</i> (2009)
	E=79; C=41	EL=30; OE=15; EE=33; CE=15	EL=OE=EE=CE	Colette <i>et al.</i> (2013)
	E=14; C=48	EL=14; EE=14; CE=48	↑ EL/EE	Dassen <i>et al.</i> (2007)
	E=31; C=29	OE=31; CE=29	OE=CE	Hevir <i>et al.</i> (2013)
	E=62; C=16	EL=34; EE=24; CE=25	*EL=EE=CE	Piccinato <i>et al.</i> (2016a)
SULT2B1	E=24; C=10	OE=24; CE=10	OE=CE	Šmuc <i>et al.</i> (2009)
	E=79; C=41	EL=30; OE=15; EE=33; CE=15	EL=OE=EE=CE	Colette <i>et al.</i> (2013)
	E=31; C=29	OE=31; CE=29	↑ OE/CE	Hevir <i>et al.</i> (2013)
	E=24; C=10	OE=24; CE=10	OE=CE	Šmuc <i>et al.</i> (2009)

*Tendency of reduced expression; ***when comparing patients in the proliferative and secretory phase. It was considered significant all mRNA expression with $P < 0.005$.

C, control patients – control patients are considered all women without endometriosis; CE, control endometrium; COC, control ovarian cyst; E, endometriosis patients; EE, eutopic endometrium from endometriosis; EL, endometriosis lesion-extraovarian; OCE, ovarian endometriotic cyst endometriosis; OE, ovarian endometriomas.

STS in epithelial cells, but not in stromal cells, of normal endometrium when compared to eutopic endometrium from women with endometriosis, suggesting cell-specific enrichment of the enzyme (Dassen *et al.* 2007). These studies used immunohistochemical analysis, and no other studies have reported protein expression data, which may reflect problems with antibody quality. Despite the controversy in protein expression data, STS activity seems to be correlated with severity of the disease suggesting that the sulphate pathway might be involved with the underlying mechanisms that contribute to the severity of endometriosis (Purohit *et al.* 2008). A clear STS activity has been described in endometriosis lesions, with a high positive correlation between protein activity and severity of the disease (Dassen *et al.* 2007). Similarly, STS activity in ectopic tissues from minimal-to-mild endometriosis was significantly lower than similar samples collected from patients affected with a moderate-to-severe form of the disease (Purohit *et al.* 2008). In the same study, however, an intriguing overall lower activity in ectopic endometrium was detected when compared to eutopic endometrium (Purohit *et al.* 2008) and a lack of differential activity between eutopic and ectopic tissues was also reported in another study (Delvoux *et al.* 2009). Using an *in vitro* approach, endometrial and endometriotic stromal cells were incubated with E2S as a STS substrate for 2 h. The result shows E2 concentrations higher in stromal cells from deep-infiltrating endometriotic lesions as compared to cells from eutopic endometrium from the same patient (Piccinato *et al.* 2016a). This finding suggests a greater efficiency of endometriotic stromal cells in metabolizing oestrogen sulphates, which might explain the ability of lesions to maintain an oestrogenic milieu. The regulation of STS activity and expression seems to be tissue specific (Dalla Valle *et al.* 2006, Zaichuk *et al.* 2007). In the endometrium, STS has been shown to be regulated by progesterone, according to menstrual cycle phases (Furusawa *et al.* 2002) with endometrium from the luteal phase of the cycle showing higher mRNA STS expression than that from the follicular phase in normal endometrium: the same observation made in endometriosis patients, for both eutopic and ectopic endometrium (Piccinato *et al.* 2016a). In the same study, STS expression was modulated by E2 and progesterone (representative steroid hormones from the luteal phase) in stromal endometriotic cells. Conversely, Dassen *et al.* found that STS mRNA expression was not affected by E2 or progesterone in explant endometrial culture (Dassen *et al.* 2007).

HSD17B subtypes

The 17- β -hydroxysteroid-dehydrogenase (HSD17B) enzymes play important roles in oestrogen biosynthesis in the sulphatase pathway. It is responsible for catalysing the oxidation and reduction of steroids, which means they activate and inactivate oestrogens, enabling them to bind with oestrogen receptors (Marchais-Oberwinkler *et al.* 2011). There are 15 HSD17B enzymes described today and with the exception of HSD17B5, an aldo-keto reductase enzyme, they all belong to short-chain dehydrogenase/reductase family and are multimeric enzymes (He *et al.* 2016). For instance, 17BHSD2 is an oestrogen inactivator (E2 to E1) and expression of 17BHSD2 may be decreased in endometriosis (Bulun *et al.* 2010). Among all HSD17B family members, HSD17B1 is considered the most important enzyme for E2 production (Zhang *et al.* 2015). Of interest, a higher HSD17B1 expression has been linked to endometriosis and the severity of the disease (Supplementary Table 5) (Tsuchiya *et al.* 2005b, Smuc *et al.* 2007, Huhtinen *et al.* 2012b).

Gene transcripts for HSD17B1 have been found upregulated in endometriosis tissues (eutopic and/or ectopic endometrium) when compared with eutopic tissue from healthy women (Dassen *et al.* 2007, Smuc *et al.* 2007, Šmuc *et al.* 2009, Huhtinen *et al.* 2012a, Colette *et al.* 2013, Delvoux *et al.* 2014), although some reports show no detectable mRNA expression for HSD17B1 in normal endometrium (Casey *et al.* 1994). Results for protein expression appear less consistent, for instance, Dassen *et al.* found higher mRNA expression of HSD17B1, but less protein expression in endometriotic tissue compared to normal endometrium (Dassen *et al.* 2007). Others, studying HSD17B1 protein expression, demonstrated higher HSD17B1 activity in ectopic endometrium compared to eutopic endometrium from the same patient (Delvoux *et al.* 2009). Another group stated that there is no protein expression in normal endometrium (Utsunomiya 2001). Disparities in findings based on different types of endometriosis (ovarian, peritoneal and deep-infiltrating) and menstrual phase have also been reported. In one study when endometriotic sites were compared, no differences were seen in HSD17B1 transcript expression between ovarian, peritoneal and deep-infiltrating endometriosis (Colette *et al.* 2013). In another study, a significant increase in HSD17B1 mRNA expression in ovarian endometriosis compared to normal endometrium was reported (Huhtinen *et al.* 2012b). The menstrual phase did not appear to influence HSD17B1 mRNA expression in eutopic tissue from endometriosis

patients or in non-endometriosis patients (Colette *et al.* 2013) and protein expression levels were also similar among different menstrual phases in both groups of women with and without endometriosis in other papers (Dassen *et al.* 2007, Colette *et al.* 2013).

Sulphotransferases

Oestrogen homeostasis is closely controlled by the balance between desulphonation and sulphation; therefore, the expression and activity of SULTs in a tissue can be considered as a mechanism that generates a reservoir of sulphated steroids that can be readily activated by STS. Overall, sulphation pathways include sulphate uptake, followed by conversion to an active sulphate in the form of 3-phospho-adenosine-5-phosphosulphate, and transfer to steroid hydroxyl groups by SULTs (reviewed by Mueller *et al.* 2015). The superfamily of steroid SULTs include members that have a direct role in oestrogen local metabolism, by catalysing the sulphonation of E1 and E2 with high affinity (E1 SULT SULT1E1, also called EST) or with low affinity (SULT1A1) (Adjei & Weinshilboum 2002); but also members indirectly modulating local oestrogen concentrations by sulphonating precursors of oestrogen formation, as for instance SULT2B1 that acts preferentially on 3 β -hydroxysteroids (Geese & Raftogianis 2001).

E1 SULT is expressed in the endometrium and although it is not a steroid-synthesizing enzyme, it has been included in this review due to its impact on intra-tissue oestrogen concentrations (Rubin *et al.* 1999). SULT1E1 has a high affinity for physiological concentrations of E2 and E1 (Honma *et al.* 2002) and is the major SULT isoform responsible for oestrogen sulphation (Zhang *et al.* 1998). SULT1E1 is, therefore, an important downregulator of oestrogen activity and can protect cells/tissues from adverse effects of excess oestrogens.

Our own data on SULT1E1 shows tendency of increased expression of the enzyme in ovarian and peritoneal endometriotic lesions, as compared to eutopic endometrium of endometriosis patients (Piccinato *et al.* 2016a). Similar results were obtained by Dassen *et al.* who reported increased expression of SULT1E1 mRNA in endometriotic lesions (without lesion type classification), as compared to that in control endometrium (Dassen *et al.* 2007). However, the same differences were not detected in the samples from 15 patients examined by Colette *et al.* (2013). We and Dassen *et al.* also reported an overexpression of SULT1E1 during the luteal phase of the menstrual cycle samples (lesions and endometrium) from

women with endometriosis, whereas cycle-dependent expression was not detected in endometrium of non-affected women (Dassen *et al.* 2007, Piccinato *et al.* 2016a). Other groups have not detected evidence of menstrual cycle phase-dependent regulation in SULT1E1 expression (Colette *et al.* 2013, Hevir *et al.* 2013) or have not controlled for this variable in their analysis (Šmuc *et al.* 2009). The only data about SULT1E1 protein expression comes from an immunohistochemical study that shows no difference in SULT1E1 expression between eutopic and ectopic endometrium (Hudeliste *et al.* 2007). However, no clear description of type of lesion was provided, suggesting that different kinds of lesions were included in the same group. Further studies with larger numbers of samples are needed to resolve the differences between these reports.

In oestrogen-sensitive tissues, such as the endometrium, the activity of SULT1E1 is generally lower than that of STS (Naitoh *et al.* 1989) promoting an increased bioavailability of active oestrogens, which may be further enhanced under pathological conditions. Although controversy still exists with regard to expression in tissue samples from women with endometriosis, reports of increased expression of SULT1E1 and co-expression of STS and SULT1E1 (Piccinato *et al.* 2016a) in endometriosis lesions as compared to control endometrium suggest that these enzymes might contribute to local generation of a reservoir of sulphated steroids that, upon deconjugation by STS, can support growth of lesions or progression of disease.

Other levels of control of oestrogen accumulation in endometriotic lesions

Metabolizing enzymes While emphasis is often placed on the role of the enhancement of E2 biosynthesis pathways, there is increasing evidence that enzymes involved in the metabolism/inactivation of oestrogens have a role in the regulation of local oestrogen homeostasis in lesions. The mechanisms by which altered oestrogen-metabolizing enzymes could potentially be involved with the pathogenesis of endometriosis ranges from reduction of local oestrogen (Piccinato *et al.* 2016a STS) to increase in the reactive oxidative species in endometriotic lesions (Hevir *et al.* 2013). Besides SULT1E1, other phase II (conjugative) metabolizing enzymes such as catechol-O-methyltransferase (COMT) and uridine diphospho-glucuronosyltransferase (UGT) and even phase I oxidative enzymes (as for instance, CYP1A1 and CYP3A4) can reduce or block oestrogen availability in endometriotic lesions, representing an important regulatory mechanism of oestrogen action.

Data from our group (Piccinato *et al.* 2016a,b,c) and reports from others (Hevir *et al.* 2013) show that enzymes classically involved in extra-hepatic oestrogen metabolism are upregulated in endometriotic lesions. It should be noted that the expression of these metabolizing enzymes may be influenced by the location of the lesion. For example, it has been reported that expression of CYP1A1 and CYP1B1 enzymes is higher in superficial lesions in comparison to eutopic endometrium or deep-infiltrating lesions (Huhtinen *et al.* 2014, Piccinato *et al.* 2016a). In addition, mRNA and protein encoded by *UGT1A1* were low or absent in eutopic endometrium, whereas it was possible to detect the enzyme in almost all types of lesions, most prominently in deep-infiltrating lesions, but also in superficial peritoneal and ovarian lesions. It is important to highlight that the metabolism of oestrogens not only alters the intensity of their action but may also alter the profile of their physiological effects in target tissues (Tsuchiya *et al.* 2005a). Although speculative, it appears that the progression of endometriosis can be influenced by the expression and activity of enzymes involved in the metabolism of oestrogens.

Cellular transport of sulphated oestrogens Sulphated steroids, such as E1S or E2S are hydrophilic, organic anions that need specific active transmembrane transport for cellular influx and efflux (reviewed by Mueller *et al.* 2015). This active cellular transport is regulated by numerous membrane-bound proteins that belong to two super-families: solute carrier (SLC) transporters and ATP-binding cassette (ABC) transporters (Roth *et al.* 2012). Very little is known about how E1S is transported into cells in the endometrium or lesions (Plaza-Parrochia *et al.* 2015). In different tissues, it seems that a variety of organic anion transporting polypeptides and SLC21 (all belonging to the SLC family) can carry E1S from the extracellular space to the intracellular space (reviewed by Secky *et al.* 2013). The efflux of E1S is, in turn, actively promoted by ABC transporters, called MRP1 and BCRP. In summary, the combined activity of transmembrane protein transporters, metabolizing enzymes and synthesizing enzymes can regulate the amount of sulphated oestrogen and, thus, the amount of bioactive oestrogen within tissues.

Summary and future directions

Endometriosis is an incurable disorder characterized by inflammation and hormone dependence. Oestrogens acting via oestrogen receptors regulate processes

including proliferation, angiogenesis, inflammation and differentiation, which are important in regulation of normal endometrium, endometrial pathologies (hyperplasia and adenocarcinoma) and have been implicated in the establishment of endometriosis lesions. *In vitro* studies using isolated cells have suggested that pro-inflammatory mediators such as PGE2 can stimulate expression of the steroidogenic enzymes detected in lesions providing a mechanism linking these two hallmarks of the disease.

Studies on endometrium and endometriosis lesions have provided compelling evidence that (intracrine) oestrogen biosynthesis associated with dysregulation of enzyme expression occurs in endometriosis. Indeed, oestrogen accumulation is defined by the balance of synthesis and inactivation/metabolism, and it seems that metabolism might play a previously underappreciated role as several key metabolizing enzymes are upregulated in endometriotic tissue. The primary sites of synthesis of the bioactive oestrogens (E1, E2) that circulate in the bloodstream are the ovarian follicles but expression of steroid-metabolizing enzymes in extraovarian sites can have a significant impact on the local concentrations of steroids in the tissue microenvironment. Expression of enzymes representing all key steps in the *de novo* steroidogenic pathway, including aromatase, has been detected. An alternative source of E1 and E2 are conjugated steroids found in the blood bathing the lesions and the discovery that the STS enzyme which uses E1S and E2S as substrate, when appropriate uptake transporters are expressed in lesions has opened up an alternative mechanism to explain the higher concentrations of E2 detected in lesions using LC/MS-MS.

Treatments focused on modulation of the enzymes that regulate local (intracrine) actions of oestrogens in lesions are being actively explored as these offers the promise of capitalizing on the proven success of regimes that suppress ovarian steroid production in reducing pain symptoms but without acting as contraceptives. Als have been effective in the treatment of breast cancer and some reports suggest AI can also relieve endometriosis-associated symptoms (Attar & Bulun 2006). Evidence of limitations on the use of AI alone or in combination for endometriosis-related chronic pelvic pain and infertility treatment have been reviewed (Pavone & Bulun 2012, Dunselman *et al.* 2014). Notably, recent data suggest new local (vaginal) routes of delivery should receive more attention and testing (Buggio *et al.* 2017). Inhibitors of AKR1C3 are an attractive option because the enzyme is active in both the steroid and prostaglandin pathways:

drugs have been developed for clinical indications including castration resistant prostate cancer and breast cancer (reviewed in Penning 2017). Bayer has developed an AKR1C3 inhibitor (BAY 1128688) for the treatment of endometriosis and this is reported in phase I completed clinical trial (ClinicalTrials.gov Identifier: NCT02434640) that led to a recently initiated phase II clinical trial. A number of STS inhibitors have been developed with the primary clinical indication being hormone-dependent cancers (Purohit & Foster 2012) and shown to be well tolerated in phase I clinical trials for breast cancer (Stanway *et al.* 2006). The STS inhibitor EMATE was shown to have an impact on lesions in mouse models (Colette *et al.* 2011), and there is a proof-of-principle report regarding the use of this STS inhibitor in combination with a progestin to treat women with endometriosis (Pohl *et al.* 2014) offering promising new therapeutic approach worthy of further investigation. To date, there have not been any studies using drugs targeting SULT1E1 or membrane transporters, but these offer additional novel targets.

In summary, there is increasing interest in the potential for targeting enzymes involved in generation of a pro-oestrogenic microenvironment in lesions as a novel fertility-sparing therapy for women with endometriosis. As new drugs become available, we can expect to see an acceleration and expansion of both basic and clinical studies and trials.

Supplementary data

This is linked to the online version of the paper at <https://doi.org/10.1530/JME-17-0297>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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