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1 **Title**

2 Menopause, Hormone Treatment and Urinary Incontinence at Midlife

3

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29

30 **Abstract**

31 Whether there is any association between urinary incontinence and menopause is the subject
32 of debate, partly due to the fact it is difficult to tell the difference between the effects of
33 menopause and those of ageing. For some time it was hoped that hormonal treatment for
34 menopause would be beneficial for urinary incontinence because there are hormonal receptors
35 in the urinary tract. The goal of this survey of current knowledge on the subject is to explore
36 thoroughly the relationship between menopause and urinary incontinence .

37 Our study is based on a review of the literature dealing with the epidemiology of urinary
38 incontinence in women aged between 45 and 60, and the effects of hormonal treatment with
39 respect to the symptoms of involuntary loss of urine.

40 Analysis of the epidemiological data drawn from large cohorts shows that on the one hand,
41 the menopause has little if any impact on the risk of urinary incontinence, and on the other
42 hand that the effects of oestrogen medication on urinary incontinence vary according to how it
43 is administered and the type of incontinence. The effect of oral hormone treatments for
44 menopause is rather negative with respect to stress incontinence. Vaginal treatment appears to
45 be beneficial for overactive bladder symptoms.

46

47 **Key-words:** *Urinary Incontinence, Stress Urinary Incontinence, Urge Incontinence,*
48 *Overactive bladder, Menopause, Hormone therapy, Oestrogen, Epidemiology.*

49

50 **No conflicts of interest to declare.**

51

52 **1. Introduction**

53 The menopause is a universal physiological event related with the drop in ovarian hormone
54 secretions (oestrogens and progesterone) that occurs as the stock of ovarian follicles is depleted.
55 Menopause is diagnosed when menstruation has stopped for 12 successive months, and the
56 average age at which it occurs is between 47 and 51 [1,2]. Its clinical expression varies very
57 considerably between socio-cultural groups and individuals [3]. These variations depend on
58 many factors, such as women's social status, their nutrition, life style (smoking) and weight,
59 not forgetting genetic factors [3]. It is difficult to draw the distinction between the effects of
60 menopause and those of ageing. In addition to the menopausal "syndrome" itself, which
61 mainly comprises vasomotor symptoms and vaginal dryness, urinary symptoms including
62 incontinence (UI) have been attributed to menopause. The hormonal dependence of the
63 genital tract tissues has been evoked in order to explain the appearance of these female low
64 urinary tract symptoms (FLUTS) at the menopause. Oestrogen receptors have been found not
65 only in the pelvic floor muscles but also in the uro-genital ligaments and detrusor muscle cells
66 along with the connective tissues and all the fascias that maintain a stable relationship
67 between the various organs [2].

68 Urinary incontinence can be defined as "the complaint of any involuntary leakage of urine"
69 [4]. The standard classification gives three main types of UI: Stress Urinary Incontinence
70 (SUI), Urge Urinary Incontinence (UUI) and Mixed Urinary Incontinence (MUI). Stress
71 urinary incontinence is characterised by involuntary loss of urine without any previous feeling
72 of a need to void, which takes place on the occasion of a physical stress (cough, lifting
73 something heavy, or any other physical activity). Urge urinary incontinence (or urgent need to
74 void) is characterised by involuntary loss of urine preceded by an urgent and irresistible need
75 to void resulting in uncontrollable leakage of urine. Mixed urinary incontinence is the
76 association in variable proportions of SUI and UUI.

77 UI may be experienced simply as a nuisance or as a real handicap [5,6]. Women frequently
78 present the symptoms of UI, but the estimates for its prevalence in the general population vary
79 widely, from 8 to 30 %. This variability is due not only to the very heterogeneous nature of
80 the populations studied but also to the varying definitions of UI used in the studies.

81 Many different factors are associated with an increased risk of UI [7]. The main of these are
82 ageing, pregnancy, childbirth, past history of pelvic and perineal surgery, obesity, and chronic
83 pathologies (diabetes, cognitive problems, etc.). There is more debate about the roles of
84 menopause and hormone replacement therapy (HRT) [8,9]. As mentioned above, it is difficult

85 to differentiate between the role of ageing and that of the menopause, and equally to
86 differentiate the true role of menopause from that of treatments instigated at the time of
87 menopause, such as HRT.

88 The relationship postulated between UI and hormone deficiencies induced by menopause is
89 based mainly on "physiological" data, i.e. the existence of (œstrogen and progestin) hormonal
90 receptors in the epithelial tissues of bladder, urethra and trigone and also in the vagina,
91 uterosacral ligaments, levator ani and puborectal muscles [10]. The other argument supporting
92 this relation is clinical observation of an increase in the prevalence of overactive bladder
93 (OAB) syndrome after the menopause. The lack of œstrogens could contribute in various
94 ways to other urinary symptoms that arise: œstrogens play a role in (i) the increase in
95 epithelial cellular trophicity in the vagina, urethra and bladder (ii) the increase in peri-urethral
96 vascularisation (an important factor for regulation of closing pressure), (iii) the increase in
97 maximum closing pressure and (iv) the increase in concentration and sensitivity of α -
98 adrenergic receptors with modification of the α -adrenergic receptors/ β -adrenergic receptor
99 ratio in favour of the α -adrenergic receptors [11-13]. Progestin receptors are also to be found
100 in the entire female genital tract, although in less constant fashion than œstrogen receptors.
101 Progestin appears to have a detrimental effect on continence, by reducing muscle tone of
102 bladder and urethra [10].

103 The aim of our review is to analyse the data in the literature with respect to the relationship
104 between menopause and UI. We present the main epidemiological data dealing with the
105 relationship between prevalence, incidence and remission of UI, and the menopause. We then
106 try to supply answers to the two main questions raised by this relationship: What
107 consequences do hormonal changes at the menopause have on UI symptoms? What
108 consequences do hormonal treatments have on continence?

109

110 2. **Methods:**

111 A review of the literature was carried out by consulting the *Medline* database entries between
112 January 2000 and June 2012. Articles were selected by cross-referencing the following
113 keywords: "*urinary incontinence, stress urinary incontinence, urge incontinence, overactive*
114 *bladder, menopause, œstrogen therapy*". In this selection priority was given to meta-analyses,
115 literature reviews, randomised controlled trials and cohort studies. The level of evidence (LE)

116 scale proposed by the *Oxford Centre for Evidence-Based Medicine* (www.cebm.net) was used
117 to class the articles selected.

118 The terminology used complies with *International Continence Society* (ICS) and
119 *International Urogynecological Association* (IUGA) recommendations.

120

121 3. Results

122 3.1. Study selection

123 Among the 488 articles initially selected during the *Medline* search, 29 articles were finally
124 retained, including 3 meta-analyses, 4 literature reviews, 5 randomised controlled trials and 12
125 cohort studies. Figure 1 gives details on this selection of articles.

126

127 3.2. Prevalence or incidence of UI according to age

128 The prevalence of urinary incontinence is proportional to age. The distribution of the various
129 types of UI changes with age. Several articles report a peak in the prevalence of SUI at midlife
130 (LE3). The majority of cases before the age of 50 are SUI, but after that age it represents a
131 minority [14]. After 60 it is mixed UI that predominates. The prevalence of UI at the time of
132 menopause varies from 8 to 27 % depending on the population studied and the definition used
133 for UI [14-17] (LE2).

134 Only a few cohort studies specifically address the menopause period (45-60 years). Mac
135 Grother *et al.* report an annual incidence of UI of 8% in a population of 108 women aged
136 between 40 and 59 in the general population [16] (LE3). Two other cohorts of women under
137 the age of 60 found annual incidence rates at 4 and 5 % [15, 17] (LE3). In another cohort of
138 2860 femmes between 40 and 60, the authors report an annual incidence rate of 6% [18]
139 (LE3). A longitudinal study of a cohort of nurses aged 36 to 55 by Townsend *et al.* found an
140 annual incidence of 7% [19] (LE3).

141 There is considerable disparity between the cohort studies concerning the annual rate of
142 remission. On the one hand Hagglund [17], Samuelsson [20], and Townsend [19] report
143 annual remission rates for UI of 4, 6, and 7% respectively (LE3). On another hand other
144 authors report higher annual remission rates, at 25 to 29% [16, 18] (LE3). These results can be
145 explained in part by the definition of remission of UI depending on the studies: complete
146 disappearance or lessening of the severity of UI symptoms.

147

148 3.3. Prevalence or incidence of UI according to menopausal status

149 The American prospective cohort *Study of Women's Health Across the Nation (SWAN)*
150 followed 1529 women, without any UI symptoms at inclusion, annually for 6 years. The
151 women were classed according to their hormonal status at the end of the study as follows: pre-
152 menopause, early peri-menopause (irregular menses), late peri-menopause (3 to 11 months
153 amenorrhoea), and post-menopause (over 12 months amenorrhoea). The peri-menopause
154 period is associated with an increased risk of UI for all types of UI together (OR= 1.52 [95%
155 CI: 1.12–2.05] in late peri-menopause) but this association disappears post-menopause (0.88
156 [0.63-1.23]). Analysis by the type of UI shows that this association with the peri-menopause
157 above all concerns UUI (2.12 [1.26-3.56] in late peri-menopause) while the association is non
158 significant for SUI (1.24 [0.75-2.05] in late peri-menopause). Analysis of frequent UI alone
159 (at least one episode of UI a week) does not show any association with early peri-menopause
160 (0.99 [0.60-1.63]), late peri-menopause (1.14 [0.51-2.54]), or post-menopause (1.10 [0.46-
161 2.64]) (LE2) [21]. In another study covering 2415 women from the SWAN cohort who were
162 incontinent (at least one episode of UI per month) at inclusion, Waetjen reports that the
163 worsening of UI symptoms observed after the menopause is not attributable to the menopause
164 itself [22] but to an increase in weight. The menopause appears to be associated with an
165 increase in weight and this would explain the increase in the prevalence of UI (LE2).

166 The study by Sherburn *et al.* of the Australian cohort of 1897 femmes, *The Melbourne*
167 *Women's Midlife Health Project*, addressed the impact of the menopause on UI symptoms.
168 Simultaneous cross-sectional and longitudinal analysis of the data did not reveal any
169 statistical relationship between UI and menopause (LE3). In the longitudinal analysis of 438
170 women from the same cohort who were followed for 7 years the menopause was not
171 associated with any increase in the incidence of UI as a whole (LE3) [15].

172 The results obtained by another longitudinal study, the *National Survey of Health and*
173 *Development (NSHD)* concerning 1211 women between 48 and 54 years of age did not find
174 any association between menopause and UUI (LE3). SUI alone was associated with the
175 hormonal status, since in this study the peri-menopause was associated with an increased
176 prevalence of urine leakage symptoms due to stress, as compared with the group of post-
177 menopausal women (OR= 1, 39 [1, 4-1, 7]) (LE3). This study, in which it is not possible to
178 distinguish clearly between the effects of age and those of menopause because there is no
179 comparison of the incidence rates between the different groups, nevertheless appears to reveal

180 an effect of ageing independent of that of the menopause with respect to the occurrence of
181 UUI or SUI (LE3) [23].

182 A large Chinese cross-sectional study of nearly 20 000 women aged 20 to 99 shows an
183 association between SUI and menopause (OR= 1, 26 [1, 04-1, 52]), even when age is taken
184 into account as a risk factor (LE4) [24].

185

186 3.4. Prevalence or incidence of UI according to hormone levels

187 A recent cohort study looked at the effect of changes in oestrogen concentrations on urinary
188 symptoms during the transition to menopause. A big drop in oestrogen levels is associated in
189 significant fashion with an improvement in UI symptoms (LE2) [25]. Moreover, analysis of
190 the annual fluctuation in endogenous oestrogen levels during the menopausal period using the
191 data from *SWAN* did not find any association with the onset of UI or worsening of UI
192 symptoms (LE2) [26]. A Swedish cohort study of 6917 women aged between 50 and 59 even
193 found a positive association between a high oestradiol level and UI (LE2) [27].

194

195 3.5. Prevalence or incidence of UI depending on menopause hormonal treatment

196 3.5.1. Data obtained from random studies of women treated for urinary symptoms

197 A meta-analysis based on eleven randomised studies of the effects of oestrogen (versus
198 placebo) on overactive bladder symptoms found a significant association between oestrogen
199 treatments and an improvement in the urinary symptoms: less pollakiuria and nocturia, fewer
200 episodes of UUI and urine leaks, improvement in the latence of the first urge to void and
201 increase in bladder capacity (LE1) [28]. However the effects vary according to the mode of
202 administration of the oestrogens. Local application (vaginal or intravesical) is associated in
203 significant fashion with an improvement in all the urinary symptoms (pollakiuria, nocturia,
204 UUI, bladder capacity). Systemic administration results in only partial improvement of these
205 symptoms, and statistically is associated only with a drop in the number of episodes of
206 incontinence and later perception of the first urge to void.

207 A review of the literature covering several randomised trials (comparisons between different
208 protocols for oestrogen treatment or versus placebo) confirms the advantage of vaginal
209 treatments in case of post-menopausal lower urinary tract symptoms, especially in the
210 presence of vaginal atrophy (LE2) [11]. The findings of recent studies of the effect of

211 oestrogens in association with anti-muscarini agents did not agree. A controlled study of 229
212 femmes presenting an overactive detrusor did not show any benefit for topical vaginal
213 oestrogen therapy associated with tolterodine versus tolterodine alone for overactive bladder
214 symptoms (LE2) [29]. Another randomised controlled trial in 80 women with overactive
215 bladder syndrome, also comparing the effect of topical vaginal oestrogen therapy associated
216 with tolterodine with that of tolterodine alone, found a significant improvement of objective
217 parameters and quality of life when oestrogens were associated with tolterodine (LE2) [30].
218 Finally, a recent randomised trial comparing the efficiency of topical vaginal oestrogen
219 therapy with that of oxybutynin for the treatment of overactive bladder syndrome found that
220 the two products were similar in terms of efficiency (LE2) [31].

221 A review of the literature covering eight controlled studies and 14 prospective non-controlled
222 studies concluded that oestrogen treatment is not efficient for SUI (LE2) [32].

223

224 3.5.2. Data resulting from secondary analyses of randomised trials in the general 225 population

226 Among the post-menopausal women enrolled in the *Womens' Health Initiative study* (WHI),
227 HRT significantly increased the incident risk at one year of all types of UI (SUI, UUI, MUI)
228 in women who were continent at the time they were included (LE2). This effect of HRT is
229 particularly distinct for SUI and less so if at all for UUI [33]. In women taking oral oestrogens
230 and progestin, the relative risk of *de novo* UI is 1.87 [1.61-2.18] for SUI, 1.15 [0.99-1.34] for
231 UUI and 1.49 [1.10-2.01] for MUI. The results are similar for women taking oestrogen alone:
232 2.15 [1.77-2.62], 1.32 [1.10-1.58], and 1.79 [1.26-2.53] respectively. In women who were
233 incontinent when included, HRT slightly increased the quantity lost (1.20 [1.06-1.36] when
234 treated using oestrogen and progestin and 1.59 [1.9-1.82] when treated with oestrogen alone),
235 and the frequency of leaks (1.36 [1.28-1.49] and 1.47 [1.35-1.61] respectively) [33].

236 Steineauer *et al.* carried out a subsidiary analysis of the *Heart Estrogen/Progestin*
237 *Replacement Study* (a double-blind randomised study assessing the effect of HRT for
238 prevention of cardiovascular risks) concerning patients with no UI at inclusion [34]. A
239 significant relationship between HRT and the onset of both UUI and SUI was found during
240 the first four months of treatment. This detrimental effect of HRT persisted throughout the 4
241 years of the study, with a cumulated additional risk of 12% and 16 % respectively for UUI
242 and SUI compared with treatment by placebo (LE2).

243 The results of these studies were included and confirmed in the Cochrane Database [35] meta-
244 analysis which covered a total of 19 313 incontinent women among whom 9417 were treated
245 by oestrogens, in 33 studies (16 of which addressed specifically SUI). There was no analysis
246 by type of UI. A worsening of UI symptoms was found when HRT was taken systemically
247 (RR= 1.32 [1.17-1.42]) (LE1). However, topical vaginal oestrogen therapy contributed
248 towards remission of UI by improving both the episodes of urge urinary incontinence (0.74
249 [0.64-086]) and pollakiuria (LE1).

250

251 3.5.3. Data obtained from cohort studies

252 The data of the *Nurses' Health Study* addressing the impact of HRT on UI in a cohort of
253 nurses aged between 30 and 55 at the time of inclusion were analysed by Grodstein *et al.* [36].
254 The occurrence of incident UI was associated in significant fashion with systemic hormone
255 therapy whatever the type of HRT and mode of administration: oral oestrogen (RR= 1.54
256 [1.44-1.65]), transdermal oestrogen (1.68 [1.41-2.00]), oral oestrogen and progestin (1.34
257 [1.24-1.44]) and transdermal oestrogen and progestin therapies (1.46 [1.16-1.84]) (LE3). The
258 overall risk of UI remained low however, with an annual incidence of 1.6%, and the effects of
259 HRT disappeared when treatment ceased.

260 A recent cohort study of post-menopausal women found an association between UI symptoms
261 and duration of oestrogen treatment. Prolonged oral oestrogen therapy (5 years or more) is
262 associated with a worsening of leakage symptoms (OR= 3.99 [1.21-13.1]) and also an
263 increase in the frequency of handicapping UI (3.97 [1.02-15.4]) [37] (LE3).

264

265 3.5.4. Data obtained from studies concerning intermediate markers

266 Certain older studies report that the use of oral oestrogens appears to increase the urethral
267 closing pressure and could thus improve SUI symptoms in 65 to 70% of women [38] (LE5).
268 Two randomised controlled trials concerning the oral route versus placebo to treat UI and
269 including 83 and 67 post-menopausal women were unable to demonstrate any effect of
270 oestrogens with respect to urodynamic parameters or urinary symptoms, whether in terms of
271 objective measurements (pad-test, cystometrography, prolifometry) or in terms of subjective
272 measurements (assessed by approved quality of life questionnaires) [39] (LE2).

273

274 3.5.5. Influence of hormonal treatment after surgery for SUI

275 Certain studies looked at the impact of oestrogen therapy when surgery is used for SUI. A
276 prospective randomised study comparing the effects of adjuvant topical vaginal oestradiol or
277 not for six months immediately after surgical correction of SUI using a sub-urethral tape
278 (TVT-O) in 183 post-menopausal patient, found that pollakiuria (2 vs. 11 %, $p=0.02$) and urge
279 urinary incontinence (3 vs. 12 %, $p= 0.01$) alone were improved by hormone therapy (LE2)
280 [40]. The objective parameters of the urodynamic tests remained unchanged in both groups
281 (LE2). In a randomised controlled trial Zullo *et al.* found exactly the same results with urge
282 urinary incontinence alone being improved by topical vaginal oestrogen therapy (LE2) [41].
283 No study of the long-term advantages of oestrogen after installation of a sub-urethral tape was
284 found.

285

286 4. Discussion

287 The results of our review concerning the link between menopause and UI do not all agree, but
288 this overview shows that the menopause has little if any impact on the risk of UI in general,
289 when confounding factors such as age or changes in weight are taken into account. It appears
290 that SUI decreases after the menopause while UUI or mixed UI increase at this time. Oral
291 HRT has a rather detrimental effect on stress urinary incontinence, by doubling the risk of *de*
292 *novo* SUI. Concerning UUI, HRT has less of an effect, which is variable according to the
293 population in question and the type of treatment. Topical vaginal oestrogen therapy is the only
294 treatment that seems to have a really beneficial effect on urge urinary incontinence or
295 overactive bladder symptoms.

296 Most of these results are drawn from longitudinal analyses of large cohorts enabling a
297 distinction to be drawn between the effect of age and that of the menopause. Longitudinal
298 studies are the only way to examine the timing, and consequently any cause and effect
299 relationship between events. Cross-sectional studies cannot assess time-dependent variables
300 such as age, weight and menopausal status. Nevertheless, the large cohort studies included in
301 this review present several problems. For example, the definition of UI is not identical in all
302 the studies because follow-up of the cohorts often started prior to the harmonisation of the
303 terminologies proposed by ICS and IUGA. The frequency of UI as a "functional complaint"
304 depends on the tools used. Moreover, few of the studies draw a distinction between the
305 various types of UI (SUI, UUI, MUI), their frequency or their severity. Finally in this type of

306 cohort, the lack of any overall assessment of incontinence risk factors (because the studies
307 were not designed initially to study this problem specifically) can result in confounding
308 biases.

309 Part of the results of this review is based on secondary analyses of randomised trials in which
310 the main objective was not to study UI but instead the cardiovascular morbidity of HRT. So
311 the level of evidence contributed by these secondary analyses is lower.

312 Certain pathophysiological data would tend to indicate a worsening of UI due to lack of
313 oestrogen. However, in contradiction with this postulate, the epidemiological data obtained
314 with the cohorts shows that the menopause has little if any effect on urinary symptoms. The
315 results of several large randomised trials in the general population reveal an aggravation of UI
316 in case of systemic HRT. This detrimental effect of HRT needs to be seen in the light of what
317 is observed during pregnancy, when an increase in the prevalence of UI is observed [42]. This
318 greater prevalence of UI during pregnancy could be explained by the increase in oestrogen
319 concentrations.

320 Topical vaginal oestrogen therapy alone appears to have a beneficial effect on overactive
321 bladder symptoms. This effect could be explained by the improvement in terms of vaginal
322 dryness and a drop in recurrent urinary infections [8,11]. The learned societies do not
323 recommend the use of oestrogens (whether or not associated with progesterone) for the
324 treatment of UI. However, in case of overactive bladder symptoms in a post-menopausal
325 woman, topical vaginal treatment may be proposed [43,44].

326

327 5. Conclusion

328 Female urinary incontinence is a complex and dynamic phenomenon, related with age and a
329 many other factors that can change with time. In order to gain greater insight, longitudinal
330 studies are necessary, with several years or even decades of follow-up in order to clarify its
331 evolution and risk factors.

332 The onset and/or worsening of UI at the menopause that is expected on the basis of
333 physiological observations is not confirmed by the results of most of the epidemiological
334 studies that mostly cover a large number of women followed up over many years. Moreover,
335 correction of the lack of oestrogen by HRT gives rise to paradoxical results that depend on the
336 type of UI and mode of administration. Systemic oestrogen therapy results in an increase in UI

337 symptoms and SUI in particular. Topical vaginal administration appears to be the most
338 beneficial by improving overactive bladder symptoms.

339

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