Ageing and reproduction: is polycystic ovary syndrome an exception?

Vieillissement et reproduction:
le syndrome des ovaires polykystiques est-il une exception ?

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Résumé

Mise au point. – Le syndrome des ovaires micropolykystiques (SOPK) est une cause fréquente d’infertilité. Malgré de très nombreuses publications qui lui sont consacrées, peu se sont intéressées au rôle exercé par l’âge sur la fertilité de ces femmes. Nous présentons le parcours de trois femmes avec SOPK et hypofertilité qui ont obtenu une grossesse au-delà de 35 ans spontanément.

Cas cliniques. – Trois femmes avec SOPK ont été suivies pendant plus de 20 ans. Le SOPK a été confirmé par des données cliniques (spatio/amenorrhée, infertilité, hirsutisme), des dosages hormonaux et une échographie des ovaires. Toutes trois ont été traitées plusieurs années avec de nombreux traitements d’induction et des réponses variables. En vieillissant, elles ont observé des cycles plus réguliers et ont débuté spontanément une grossesse plus de 5 ans après arrêt de tout traitement d’induction et malgré une augmentation de leur poids dans chaque cas à 39, 40 1/2 et 36 ans.

Conclusions. – Ces observations cliniques suggèrent une augmentation de la fertilité avec l’âge chez des femmes ayant un SOPK. L’impact positif de l’âge sur la régularité des cycles a été récemment publié mais pas l’amélioration de la fertilité. Le vieillissement ovarien entraîne une diminution de la cohorte folliculaire chez les femmes normales et celles ayant un SOPK, en rapport avec une baisse de l’inhibine B et de l’hormone anti-müllerienne (AMH). Les taux plus faibles d’inhibine B entraînent une riposte de FSH avec élévation du taux de FSH par follicule entraînant une meilleure maturation folliculaire à un âge plus avancé. Les cycles plus réguliers et potentiellement ovulatoires ont été confirmés chez ces femmes de plus de 35 ans par la survenue d’une grossesse spontanée, ce qui n’était pas survenu auparavant.

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Abstract

Background. – Polycystic ovary syndrome (PCOS) is a frequent cause of infertility. Despite an impressive number of reports, few have evaluated the influence of age upon fertility. We present the outcomes of three infertile women with PCOS who achieved spontaneous pregnancies when ageing.

Case reports. – Three patients with PCOS were monitored for more than 20 years. PCOS was confirmed by clinical data (oligo/amenorrhoea, infertility, hirsutism), hormonal measures and ovarian ultrasonography. All three infertile patients were treated for several years using numerous ovulation induction protocols with varying responses. When ageing, they gained more regular cycles and spontaneously became pregnant at 39, 40 1/2 and 36 years of age, more than 5 years after induction treatment was stopped, and in spite of increasing weight in each of them.

Conclusions. – These clinical observations suggest improved fertility in some PCOS ageing women. The positive impact of ageing on cycle regularisation in PCOS has recently been claimed but the fertility outcome was not evaluated. Ovary ageing results in diminution of the follicular cohort in both normal and PCOS women, associated with decreased inhibin B and anti-müllerian hormone (AMH) levels. Lower inhibin B levels induce FSH enhancement, with a rise in FSH rate per follicle which may determine better follicle maturation, regular and ovulatory cycles in PCOS ageing women. The best proof of this improved fertility was the occurrence of spontaneous pregnancies which never occurred previously.

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1. Introduction

Polycystic ovary syndrome (PCOS), one of the most common endocrine disorders estimated to affect at least 5% of women of reproductive age, is a heterogeneous condition of multifactorial aetiology, with a wide variety of clinical symptoms [20,35]. Therefore a single diagnostic criterion is not sufficient and the recent Rotterdam consensus following NIH 1990 definition has proposed three criteria: oligo or anovulation, clinical and/or biological signs of hyperandrogenism, ultrasound typical aspect of polycystic ovaries and exclusion of other causes of hirsutism [37].

An important aspect of PCOS is infertility, which includes oligo/anovulation and increased miscarriage rate (approximately one-third of all pregnancies, twice as high as in normal women) [6]. The underlying mechanisms probably involve both intra- and extra ovarian regulator factors. Women with PCOS usually have higher LH and low–normal FSH levels in the early follicular phase compared to normal women [9]. Anovulation in these women is partly related to the relatively low FSH levels, which becomes greater beyond 40 years. These hormonal and US evaluation is shown in Table 2. In March 1997 (at 39 years of age) in spite of persistent oligomenorrhoea (90–150 days) and of increasing weight (108 kg), and without any treatment during the preceding 5 years, she had a spontaneous pregnancy and gave birth to a healthy little girl. Regular menstrual cycles occurred after delivery.

Patient 2 was born in 1958. Menarche occurred at the age of 12 years, and after 1 year she consulted for amenorrhoea. A positive response to progestin (Duphaston®) was followed by oligomenorrhoea (6–16-week intervals). She was obese (89 kg for 165 cm, BMI 32.5 kg/m²), hirsute (Ferriman score 16) and hypertensive (150/90 mmHg at the first consultation). In 1982 (at 24 years of age) she wanted to become pregnant. Biological tests revealed high LH, normal FSH (LH/FSH > 4), normal prolactin, and high androgen levels (Table 1). Morphological investigations of the reproductive tract were normal. Several cycles of clomiphene citrate (Pergotim®) alone or associated with gonadotrophins (Humegon®) remained unsuccessful in spite of confirmed ovulation. At the age of 31, after a treatment with purified uFSH (Metrodine®) and hCG, pregnancy was achieved but miscarriage occurred in the 10th week of gestation. In 1991 she started a new treatment with purified uFSH (Metrodine®) combined with dexamethasone (Dectanyt®). She had three ovulatory cycles but no pregnancy. After several unsuccessful treatments during 3 years, she became depressed and gave up. A summary of her longitudinal hormonal and US evaluation is shown in Table 2.

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2. Case reports

Three patients with confirmed PCOS consulted the Fertility Centre of Tours between 1981 and 1986 wishing to become pregnant. The diagnostic criteria at that time were based upon clinical data (oligomenorrhoea and anovulation, infertility, hirsutism); ultrasound features (micropolycystic ovaries), and hormonal results (high LH, relatively low FSH, and high androgen levels, performed the third day of the menstrual cycle) (Table 1). Their partners’ infertility was excluded by normal sperm counts. Pituitary or adrenal causes of anovulation and hirsutism were excluded (normal PRL, TSH, and IGF1 secretion, normal 17 OH progesterone levels after corticotrophin stimulation test). The progestin test was positive in all three patients.

Patient 1 was born in 1958. Menarche occurred at the age of 12 years, and after 1 year she consulted for amenorrhoea. A positive response to progestin (Duphaston®) was followed by oligomenorrhoea (6–16-week intervals). She was obese (89 kg for 165 cm, BMI 32.5 kg/m²), hirsute (Ferriman score 16) and hypertensive (150/90 mmHg at the first consultation). In 1982 (at 24 years of age) she wanted to become pregnant. Biological tests revealed high LH, normal FSH (LH/FSH > 4), normal prolactin, and high androgen levels (Table 1). Morphological investigations of the reproductive tract were normal. Several cycles of clomiphene citrate (Pergotim®) alone or associated with gonadotrophins (Humegon®) remained unsuccessful in spite of confirmed ovulation. At the age of 31, after a treatment with purified uFSH (Metrodine®) and hCG, pregnancy was achieved but miscarriage occurred in the 10th week of gestation. In 1991 she started a new treatment with purified uFSH (Metrodine®) combined with dexamethasone (Dectanyt®). She had three ovulatory cycles but no pregnancy. After several unsuccessful treatments during 3 years, she became depressed and gave up. A summary of her longitudinal hormonal and US evaluation is shown in Table 2.

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Patient 2 was born in 1959. Menarche at 14 years of age, oligomenorrhoea (60 days) with anovulation was followed by amenorrhoea. She was not hirsute (Ferriman score 6) or overweight (BMI 24 kg/m²). She first consulted for infertility in 1986, at the age of 27. Biological tests revealed a high LH/FSH ratio (> 2), normal PRL, and high androgen levels (Table 1). Treatment with clomiphene citrate (Clomid®), in progressive doses, allowed her to achieve her first pregnancy after seven cycles. She delivered a healthy baby girl at term. At 30 years of age, she wanted a new pregnancy. After five cycles with clomiphene citrate (Clomid®) and uFSH (Metrodine®), a second pregnancy was achieved and she gave birth to a healthy little boy. She again presented oligomenorrhoea which was treated with oral contraceptive. A summary of her longitudinal hormonal and US evaluation is shown in Table 2. In March
2000, at the age of 40, she started to gain weight (61 kg vs. 56 kg, BMI 27 kg/m²) and stopped her oral contraception. Six months later she spontaneously became pregnant. She did not want further pregnancy and had a voluntary abortion.

**Patient 3**, born in 1961, consulted wishing to become pregnant at 20 years of age. Menarche had occurred at 16 1/2 years, with oligomenorrhoea (4–6 months). She was hirsute (Ferriman score 14), with normal weight (BMI = 20 kg/m²). LH was high, with normal FSH, and LH/FSH ratio > 3. Prolactin was normal and androgen levels were high (Table 1). She first tried ovulation induction with clomiphene citrate (Clomid®) remained unsuccessful. In June 1986, at 25 years of age, she had bilateral salpingolysis for post surgery adhesions, followed by a new course of clomiphene citrate. Pregnancy was achieved and she gave birth to a healthy little girl in May 1987. She used contraception (Ovanon® then Diane®), which was stopped in February 1988. New treatment with clomiphene citrate combined with dexamethasone resulted in pregnancy but she had a spontaneous abortion followed by contraception. In 1990, at 30 years of age, she again wished to become pregnant. Basal levels of gonadotrophins were: LH 19 IU/l, FSH 5 IU/l. In September 1991, after treatment with clomiphene citrate combined with dexamethasone, she became pregnant but spontaneously aborted. She gave up infertility treatment. Five years later, after achieving more regular cycles (35–38 days) and in the absence of any treatment, she became pregnant. Her weight was 55 kg (+ 7 kg). However, she no longer wished pregnancy and had voluntary abortion followed by oral contraception. A summary of her longitudinal hormonal and US evaluation is shown in Table 2.

All three patients had no spontaneous pregnancy and needed infertility treatment. The response was variable: failure during various periods of time followed by normal pregnancy after several treated cycles (patients 2 and 3) or miscarriage (patients 1–3). After 35 years of age and more than 5 years free of infertility treatment, they spontaneously conceived. A summary of treatment and fertility outcome is shown in Table 3.

### 3. Discussion

PCOS is the most common cause of infertility in women. In view of the current knowledge of decreasing fertility with age in normal women and the poor fertility of young women with PCOS, the spontaneous late pregnancies observed in our patients look like a paradox.

Numerous theories have tried to identify the primary defect of anovulation in PCOS, leading to a wide range of treatments. LH excess and a higher LH/FSH ratio have been found to induce impaired oocyte maturation and greater miscarriage rate [36]. Enhancement of endogenous FSH by administration of...

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### Table 1
Clinical and biological data at the time of diagnosis

<table>
<thead>
<tr>
<th>Clinical data</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menarche age (years)</td>
<td>12</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Secondary amenorrhoea</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cycle duration (days)</td>
<td>45–120</td>
<td>60–90</td>
<td>120–180</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165</td>
<td>153</td>
<td>155</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>89</td>
<td>56</td>
<td>48</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32.5</td>
<td>24.0</td>
<td>20.0</td>
</tr>
<tr>
<td>FSH (IU/l)</td>
<td>3.8–12.6</td>
<td>5.5</td>
<td>10.0</td>
</tr>
<tr>
<td>Testosterone (nmol/l)</td>
<td>23.1–37.2</td>
<td>2.1</td>
<td>2.8</td>
</tr>
<tr>
<td>Delta4-Androstenedione (nmol/l)</td>
<td>20–70</td>
<td>11.6</td>
<td>25</td>
</tr>
<tr>
<td>Ultrasonography (Rotterdam criteria)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

* Normal values for the follicular phase.

### Table 2
Evolution of hormonal levels and ultrasonography

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>FSH (IU/l)</th>
<th>LH (IU/l)</th>
<th>Testosterone (ng/ml)</th>
<th>Delta4 A (ng/ml)</th>
<th>Ultrasonography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>2.9</td>
<td>6.9</td>
<td>0.6 (N &lt; 0.5)</td>
<td>2.3 (N &lt; 2.2)</td>
<td>ND</td>
</tr>
<tr>
<td>31</td>
<td>5.5</td>
<td>25</td>
<td>0.7 (N &lt; 0.5)</td>
<td>6 (N &lt; 3.5)</td>
<td>PCO*</td>
</tr>
<tr>
<td>34</td>
<td>5</td>
<td>20</td>
<td>0.9 (N &lt; 0.5)</td>
<td>6.7 (N &lt; 3.5)</td>
<td>PCO*</td>
</tr>
<tr>
<td>Patient 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>11</td>
<td>21</td>
<td>0.74 (N &lt; 0.5)</td>
<td>3.7 (N &lt; 2.7)</td>
<td>PCO</td>
</tr>
<tr>
<td>29</td>
<td>2.7</td>
<td>5.5</td>
<td>0.55 (N &lt; 0.5)</td>
<td>2.6 (N &lt; 2.5)</td>
<td>ND</td>
</tr>
<tr>
<td>31</td>
<td>3.1</td>
<td>6.3</td>
<td>0.67 (N &lt; 0.5)</td>
<td>3.2 (N &lt; 2.5)</td>
<td>PCO</td>
</tr>
<tr>
<td>Patient 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>5.4</td>
<td>14.3</td>
<td>0.7 (N &lt; 0.5)</td>
<td>13 (N &lt; 7)</td>
<td>Cuneiform resection: PCO*</td>
</tr>
<tr>
<td>21</td>
<td>4.5</td>
<td>16</td>
<td></td>
<td></td>
<td>ND</td>
</tr>
<tr>
<td>24</td>
<td>4</td>
<td>21</td>
<td>0.65 (N &lt; 0.5)</td>
<td>2.9 (N &lt; 3.5)</td>
<td>PCO*</td>
</tr>
<tr>
<td>30</td>
<td>5.2</td>
<td>19</td>
<td></td>
<td></td>
<td>PCO*</td>
</tr>
<tr>
<td>35</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PCO*</td>
</tr>
</tbody>
</table>

* Multiple peripheral follicles and stromal hyperplasia.

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clomiphene citrate or exogenous FSH is intended to correct the gonadotrophin imbalance. Approximately 70% women respond to clomiphene citrate but only 40–60% become pregnant within 6 months [21]. Theoretically, purified FSH, which decreases the LH/FSH ratio should be more effective than traditional human menopausal gonadotrophins (hMG), but in practice the results are comparable [2]. The best results are obtained when the various protocols are given by the step-up low-dose approach [44].

Hyperandrogenism is a common feature in PCOS. Intra-ovarian hyperandrogenism seems to promote early follicular growth leading to a follicle 2–5 mm excess. Small follicles excess is responsible for increased antimüllerian hormone (AMH) levels, which would induce partial resistance to FSH action [10,23,29]. Reduction in the number of the follicles (by cuneiform resection or laparoscopic diathermy), improves fertility by inducing a new hormone balance with a decrease in androgen levels, followed by a fall in LH and a rise in FSH [3, 35]. No significant difference in fertility outcome was reported in a controlled trial that compared laparoscopic surgery with exogenous gonadotrophin treatment [1].

The influence of age (and ageing) in PCOS women, rarely discussed in the literature, has been presumed to be negative upon fertility outcome [44].

Our three patients consulted for infertility at a young age (between 20 and 27 years). Two patients were hirsute, one of them being also obese. Hyperandrogenism, ultrasound evidence of polycystic ovaries, and high LH/FSH ratio were present in all three patients. They all needed more than one treatment regimen for induction of ovulation, starting with clomiphene citrate and followed by different FSH preparations, which induced varying responses. Cuneiform resection was unsuccessful in the third patient due to pelvic adhesions.

It should be emphasised that these women had great difficulties to procreate and no spontaneous pregnancy occurred before the age of 35. After this age menstrual cycles became more regular and they spontaneously conceived in spite of physiological weight increase. Each pregnancy occurred at a significant interval of time after the last treatment (at least 5 years) and therefore they could not be attributed to a late effect of the treatment (Table 3). Due to the unexpected occurrence of pregnancies, few hormonal data could be obtained.

Ovarian ageing is an irreversible process. In normal women, the most sensitive clinical sign is the progressive occurrence of menstrual irregularities [5,34]. Follicles number declines in a bi-exponential manner, faster after the age of 37.5, leading to the menopausal threshold at 51 [18,32]. Fertility decreases in parallel with the reduction in follicle numbers.

Secondary to the physiological ovarian failure, FSH began to increase in the early follicular phase at the age of 35 [12], whereas LH secretion does not change until the age of 45 [32]. AMH levels, which are strongly correlated with the number of antral follicles, decline with age in normo-ovulatory women [13]. Inhibin B is considered as the earliest marker of decline in the number of follicles [24,34,42], and the major cause of FSH increase [33].

Histological studies of young polycystic ovaries have found twice the number of primary follicles compared to normal age-matched ovaries [4,15,39] and up to sixfold increase in the number of primordial and primary follicles in anovulatory women with PCOS compared to normal regularly cycling women [40]. Although the final stages of maturation in PCOS follicles are arrested, these follicles are not atretic and remain sensitive to FSH stimulation in vivo [26] and in vitro [38]. The decrease in follicles number in polycystic ovaries follows the same pattern as in normal ovaries, with a significant reduction with age [4]. Having a significantly larger follicular pool, women with PCOS are unlikely to undergo a rapid depletion of their ovarian reserve [28]. This assumption is sustained by a recent longitudinal study which demonstrated that the decline of AMH with age is less obvious in PCOS women, favouring a longer reproductive life in these women [27].

It has been claimed that women with PCOS have a late menopause [6] and gain regular cycles when they grow older [16]. Achievement of regular cycles, which we too did observe in our clinical practice, was definitely assessed in PCOS ageing women with [11] or without [16] previous wedge resection. Older PCOS women with regular cycles have a lower number of follicles and lower androgen levels compared to those with irregular cycles [14,17]. Nevertheless, none of these studies evaluated the fertility outcome.

Our three patients not only gained regular cycles when ageing but also improved their fertility. Since they denied further treatment and follow-up years before the occurrence of these spontaneous late pregnancies, we were not able to perform a regular hormonal evaluation and can only speculate, in view of the present literature data, about the possible causes of the restoration of fertility:

• Decrease of the follicular pool: present in PCOS similarly to normal women, with a decrement of inhibin B, which facilitates more regular and presumably ovulatory cycles. Starting from a larger follicular pool, this depletion is slower, as proven by higher and more lasting AMH levels, with a prolonged reproductive life span [27].

Table 3
Fertility outcome
Évolution de la fertilité

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Result</td>
<td>Age</td>
</tr>
<tr>
<td>CC 24</td>
<td>(–)</td>
<td>27 G</td>
</tr>
<tr>
<td>CC + DXM Ø</td>
<td>Ø</td>
<td>27 (–)</td>
</tr>
<tr>
<td>CC + FSH 29 (–)</td>
<td>Ø</td>
<td>30 Ø</td>
</tr>
<tr>
<td>FSH + hCG 31 M (10 w)</td>
<td>Ø</td>
<td>22 (–)</td>
</tr>
<tr>
<td>Surgery</td>
<td>Ø</td>
<td>Ø</td>
</tr>
<tr>
<td>Spontaneous pregnancy</td>
<td>39 G</td>
<td>40 1/2 A</td>
</tr>
</tbody>
</table>

CC: clomiphene citrate; DXM: dexamethasone; Ø: not done; (–): no response; M: miscarriage; A: voluntary abortion; G: successful pregnancy, delivery of a girl; B: successful pregnancy, delivery of a boy.

* Age when the last treatment was performed.
Better follicular maturation: both normal and PCOS women have a negative correlation of androgen levels with age (normal women at 40 years of age have half the testosterone levels than in their 20s) [30,46]. Decrease in free androgen levels is related to reduced androgen secretion and SHBG increase [25] and contributes to a better follicle maturation as shown by in vitro maturation (IVM) [7]. BMI increases with age might favour a decrease in inhibin B [4,43]. This inhibin B diminution could induce a relative increase in FSH, allowing late follicle maturation.

In summary, our clinical observations suggest improved fertility in ageing PCOS women. As they gain regular cycles when growing older, this regularisation might further be associated with normal ovulation. The late occurrence of spontaneous pregnancies following several complex treatments supports this hypothesis. Only a longitudinal study of a population of ageing women with PCOS could evaluate whether this increase in fertility is rather frequent, but this paradoxical fact requires future interest.

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