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Continuous Contraceptive Use Combined with Overweight or Obesity Triggers the Risk of Surgery Due to Leiomyomas

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Abstract

Background: Uterine leiomyomas or fibroids are the most common bening tumours of the myometrium and the most common neoplasia of the female genital tract and being the most common indication for hysterectomy as the predominant treatment option. We have conducted a study in order to identify the hormonal factors associated with risk of uterine leiomyomas requiring surgery in premenopausal women.

Methods: Case-control study in a Caucasian spanish population conducted with women attending the gynecology departments of two hospitals in Canary Islands. A total of 577 women who underwent hysterectomy or myomectomy for uterine leiomiomas in a four years period at both hospitals were included as cases and 644 women with intact uteri and free of uterine leiomyoma as confirmed by ultrasound diagnosis served as control subjects. Age, menarche, number of term pregnancies, height, weight, history of oral contraceptive and in vitro fecundation treatment was recorded at baseline. For cases, gynaecological data include number of leiomyomas, location, size and diagnosis of polymyomatosis. Logistic regression equation was applied to estimate the chance of suffer surgery due to leiomyoma.

Results: In vitro fecundation increase 14 (95%CI: 8-21) times the risk of surgery due to uterine leiomyomas. Overweight and obesity increased the risk of surgery over 7 (95%CI: 4-11) and 11 (95%CI: 5-19) times respectively. Every month of contraceptive intake increases in 29% (95%CI: 5%-219%) the risk of surgery. Finally, the risk associated with ovarian activity was near 7 (95%CI:2-14) times and each additional year of age increases the risk or leiomioma surgery by 8% (95%CI:4%-9%).

Discussion: Based on our results, at age 50 the probability of surgery because leiomyomas for women with normal weight increases four times more than at 20 years old. Fixing the age, the probability of needing surgery increased from 50 to 60 percent for overweight to obese women. Fixing age and weight, after a year of contraception use the probability of surgery because leiomyoma raise to two-thirds, and is nearly 100% in case she is 50 years old and overweight or obese.

Conclusion: Age increase, prolonged contraceptive use, in vitro fecundation, overweight and obesity, lead to a higher and more prolonged exposure of the uterus to steroid hormones, cumulative effect leading to increased risk of growth of already existing fibroid or the formation of new ones in those uteri at risk of developing leiomyomas, that contributes to increase the risk of surgery for fibroids.

Keywords: Uterine leiomyomas; Hysterectomy; Risk factors

Introduction

Uterine Leiomyomas (UL) or fibroids are the most common benign tumours of the myometrium and the most common neoplasia of the female genital tract [1,2]. The incidence in the population varies with age, being 60% on African-American women at age 35 which increases to over 80% by age 50, while Caucasian women have an incidence of 40% and almost 70% respectively [3]. Leiomyomas are symptomatic in 50% of the cases and they have a significant level of morbidity manifesting as a spectrum of clinical symptom [4]. These include urinary incontinence, constipation, abdominal pain, impairment of fertility, menorrhagia and difficult and extended menstrual periods that can lead to anemia [5,6]. Such high morbidity results in UL being the most common indication for hysterectomy, which is the predominant option in North America, Europe and Japan [3,7,8]. Surgical treatment, work loss associated to heavy menstrual bleeding, problems associated with infertility and complications during pregnancy made the cost associated to this disease being extraordinarily high. In fact, the total direct cost associated with hysterectomies and myomectomies in 2000 in the United States was $2.1 billion [7].

Among the factors predisposing for the development or UL, genetic susceptibility may explain both, the higher prevalence rate among African-American women and the 2.5 times increase risk of developing UL for the first-degree relatives of women with myomas [3]. The initiation event for these tumors is unclear and may be due to genetic or epigenetic alterations [9-12]. However, it is generally accepted that leiomyomas are steroid hormone-dependent tumours [1,13], although their action in the aetiology and/or development of leiomyomas has not been fully clarified. Their hormone dependence is based primarily on clinical observations, as they are rarely observed before puberty, are more prevalent during the reproductive years, enlarge during pregnancy and regress during menopause, ovariectomy and other hypoestrogenic conditions [3,14-16]. In addition, they show increased estrogen-receptor gene expression and enhanced sensitivity to estrogen stimulation compared to normal myometrium [17]. Progesterone seems to favor the mitogenic activity of leiomyoma cells in culture [18] and also promotes leiomyoma cell survival through up-regulating Bcl-2 protein expression [19]. Therefore, all those factors that affect the hormonal environment throughout women's lifespan such as early menarche, parity, obesity, Oral Contraceptive use (OC) and In Vitro Fertilization treatment (IVF) should be carefully considered as potential risk factors for the occurrence of UL.

The epidemiological data on risk factors associated to fibroid prevalence are limited, especially in European population. In Spain, where epidemiological studies are lacking, data from the National Institute of Statistics show that UL account for 49% of the benign tumors that cause hospitalization and assuming similar costs with others European countries, the cost associated with UL would also be substantial [20]. In addition, data from hospital physicians from our group point to an increase in the number of hysterectomies caused by UL and a decrease in the age of patients undergoing surgery for this condition. Conflicting data have emerged regarding the roles of Oral Contraceptives (OC) use and obesity and the risk of uterine leiomyomas [21,22]. We have conducted a case-control study in a spanish population in order to identify those hormonal factors associated with risk of UL requiring surgery in premenopausal women.

Material and Methods

This is a case-control study conducted with patients attending the gynecology departments of the Hospital University of the Canary Islands (HUC) and the USP Hospital La Colina, both in Tenerife, and was approved by the appropriate Institutional Review Board. All study procedures were in accordance with the ethical standards set forth in the revised Declaration of Helsinki. Inclusion criteria for the study were caucasian Spanish women with residency in Canary Islands, Spain, authorization of use of medical records for research and absence of gynecologic cancers. A total of 577 women who underwent hysterectomy or myomectomy for uterine leiomiomas in a four years period at both Hospitals were included as cases. In addition, 644 women with intact uteri and free of uterine leiomyomata as confirmed by ultrasound diagnosis served as a pool of control subjects.

For the cases, gynecological data include number of leiomyomas, location, size (cm) and diagnosis of polymyomatosis. Leiomyomas diagnoses as 'Rapid growth' were excluded. Detailed information on age, menarche, number of term pregnancies, height, weight, history of oral contraceptive and IVF treatment was recorded at baseline. These data were confirmed at the time of study entry by telephone interviews with the patient. Body Mass Index (BMI) was calculated as weight (in kilograms) divided by the square of height (in meters). The sample was stratified by weight status into normal weight (BMI≤24.9 kg/m^2), overweight (25≤BMI≤29.9 kg/m^2) and obesity (BMI≥30 kg/m2). Patients treated with IVF had undergone the long protocol that includes induction of ovulation with leuprolide acetate and GnRH agonist in the middle of the luteal phase (days 21-22 of the cycle), with an initial dose of 0.5-1.0 mg/day, by intravenous or intranasal administration. This dose was reduced to half on appearance or menstruation before starting stimulation with gonadotropins, FSH or FSH-LH, at 200-300 IU daily for 11 days, plus a dose of HCG 10,000 IU. Then, 24 hours after removal of the oocyte, 200 IU progesterone was administered every 12h for 48 hours, and finally every 8 hours for 18 days.

Data Analysis

Sample characteristics were described summarized variables with the relative frequencies of their component categories and its 95% confidence intervals. To assess differences between cases and controls, Pearson's χ^2 test was performed for nominal and scale variables converted in nominal ones. Time variables were summarized with median(P_0-P_{95}) and compared using Mann-Whitney U test. Odds Ratios (OR) were estimated by binary logistic multivariate regression analysis. All the studied variables were included in the regression analysis, regardless of the significance results previously obtained in the univariate comparisons. We adjusted logistic models by backward strategy and Wald's criteria. With the logistic regression equation obtained we estimate the chance of suffer surgery due to leiomyoma. All tests were two-tailed at 0.05 significance level and calculations was carried out using SPSS 21.0.

Results

The sample consisted of 1221 patients whose characteristics are shown in (Table 1). The age of menarche as a marker of endogenous gonadal hormones exposure was 12(7-17) years. The mean of BMI for the whole sample was 23(4) kg/m^2 which is the normal weight range and 80% belong to this category, however 14% were classified as overweight and 6% as obese. Twenty two percent had used oral contraceptives continuously, with being 1 (1-120) months and 3% had received treatment for in vitro fertilization.

Characteristic	Relative frequency (95%CI)
Age (years old range)	
14-38	52(49-55)
39-53	39(36-42)
54-84	9(7-11)
Ovarian activity	
Menarche (mean years old)	12(7-17)
Menopausal	11(9-12)
Parity	
Nulliparous	62(59-66)
Primiparous	16(13-18)
Multiparous	22(19-24)
BMI (kg/m^2)	
<24.9	80(78-82)
25.0-29.9	14(13-17)
>29.9	6(5-8)
Hormonal Treatment	
IVF	3(2-4)
ACO	22(19-24)
OC duration use (months)	1(1-120)

Table 1: Characteristics of the entire sample (1221 subjects).

The relative frequencies and its 95% confidence intervals among cases and controls for all the variables analyzed are summarized in (Table 2).

Characteristic	Relative frequency (95%CI)		P-Value
	Cases (n=577)	Controls (n=644)	
Age (Years old range)			
14-38	30(26-34)	71(67-74)	
39-52	61(57-65)	20(17-23)	<0.001
53-84	9(7-12)	9(7-11)	
Ovarian activity			
Menarche (mean years old)	12(7-16)	12(7-17)	0.0732
Menopausal	11(9-14)	10(8-12)	0.3961
Parity			
Nulliparous	52(44-59)	66(62-69)	
Primiparous	15(10-21)	16(13-19)	<0.001
Multiparous	33(26-40)	19(16-22)	
BMI (kg/m^2)			
<24.9	48(40-55)	88(85-90)	
25.0-29.9	32(25-40)	9(7-11)	<0.001
>29.9	20(14-26)	3(2-5)	
Hormonal Treatment			
IVF	5(4-7)	1(0-2)	<0.001
ACO	22(19-26)	21(18-24)	0.6
Duration OC use (months)1b	12(1-155)	1(1-5)	<0.001

Table 2: Results of the univariate comparison of frequency of factors between cases with uterine leiomyoma and its controls.

The proportion of women in the younger age group (14-38 years old) was 2.3 times higher in controls. On the contrary, in the forth and beginning of the fifth decade of life, the proportion of women with leiomyomas who undergone surgery increased threefold while the number of women in the menopausal age remained the same in both groups. These differences reach statistical significance. The proportion of women with two or more children was 1.7 higher in cases that in controls, while nulliparous were slightly higher in controls and no differences were observed for primiparous. With respect to weight, differences were observed for the three categories, with almost double the number of controls under normal weight, and 3.5 and nearly 7 times higher the number of patients operated by leiomyomas, who are overweight and obese, respectively. The BMI was 26(4) kg/m2 for UL patients and 23(3) kg/m2 for controls with significant differences between groups. No differences were observed between groups for age at

menarche. Regarding hormonal treatment, the number of patients who received IVF treatment was 5% versus only 1% of women from the control group, which differs significantly. Interestingly, although the proportion of women taking oral contraceptive was similar in both groups the duration of the hormonal intake was clearly larger for the cases. The results of adjusting logistic regression analysis over all variables are shown in (Table 3).

Factor	OR (95%CI)	p-Value
Overweight (respect to normal)	6.58 (3.75-11.06)	<0.001
Obese (respect to normal)	10.57 (5.11-18-95)	<0.001
Not menopausal	6.93 (2.38-14.29)	<0.001
Each year of age	1.08 (1.04-1.09)	<0.001
Every other month with ACO	1.29 (1.05-3.19)	<0.001
Receiving assisted reproduction treatment	14.28 (8.08-21.60)	<0.001

Table 3: Odds ratios of surgery due to leiomyoma estimated according to the multivariate logistic regression analysis.

These estimations showed that IVF treatment increase 14 times the risk of surgery due to uterine leiomyomas compared to control group. Both overweight and obesity increased the risk of surgery over 6 and 10 times. The duration of contraceptive use was also associated with uterine leiomyoma requiring surgery, and every month of contraceptive intake increases in 29% the risk of surgery. Finally, the risk associated with ovarian activity was near 7 times and each additional year increases the risk or leiomioma surgery by 8%.

The general mathematical relationship to estimate the probability of develop a chirurgical leiomyoma according the logistic model has the form shown below

$$P_{risk}=\frac{1}{1+\frac{1}{e^{-6.969+1.883xOverweight+2.358xObesity+1.936xMenopause+0.076xAge+0.257xMonth\_OC\_USE+2.659xFIV}}}$$

According this model as age increases, the likelihood of needing surgery in women with fibroids increases concomitantly (Figure 1A). In this sense, between the fourth and fifth decade of life, a period where surgery due to leiomyomas is very frequent, the risk of needing surgery increases almost two-fold, from 12% to 23% for women under normal weight. Interestingly, the risk of surgery increases substantially if the woman is overweight or obese, with a 4-fold increase at age of 40 and almost 3-fold increase at age of 50, respectively. Moreover, if we include in the analysis oral contraceptive intake during 12 months, the probability of needing surgery in the same decade for women under normal weight increase progressively from 75% to 86%, but its nearly 100% in overweight and obese women (Figure 1B). Virtually the same pattern as oral contraceptive use is observed for women with leiomyomas who have undergone in vitro fertilization treatment (Figure 1C). The worst scenario is observed for women who have taken oral contraceptive for 12 months and also have received treatment for in vitro fertilization. In this case, women over 30 years old have a probability of needing surgery close to 100%, regardless of their weight (Figure 1D).

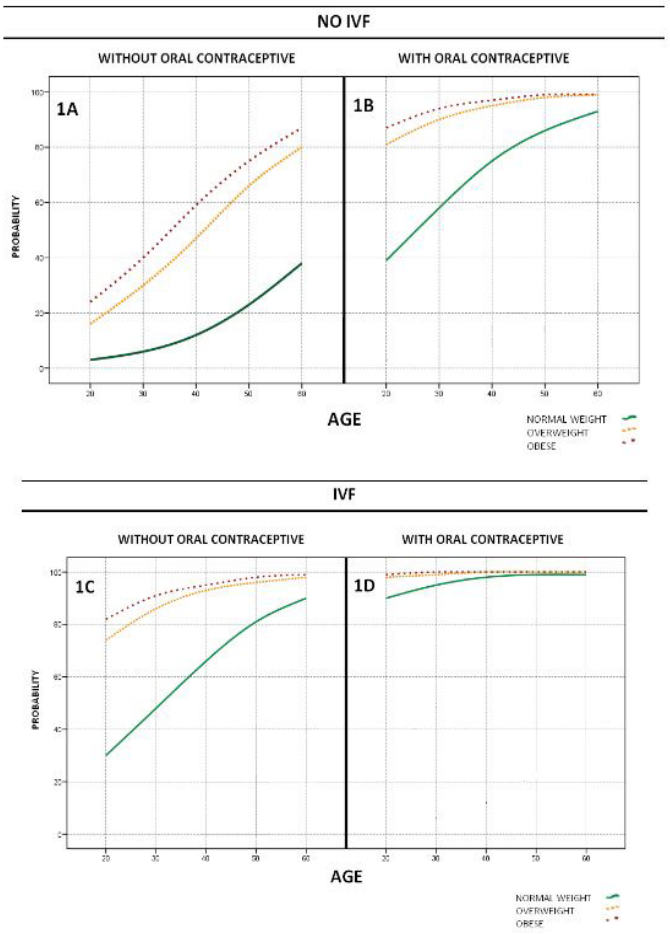

Figure 1(A-D): The probability of surgery due to leiomyomas according to the logistic analysis considering age and BMI **(1A)**; age, BMI and oral contraceptive use at least 12 months **(1B)**; age, BMI and IVF treatment **(1C)** and age, BMI, oral contraceptive use at least 12 months and IVF treatment **(1D).**

Discussion

In this study we have initially compared internal (age with ovarian activity, body max index and parity) and external (contraceptive use and in vitro fertilization) hormonal conditions, between women without leiomyomas, as assessed by ultrasound, and women who have experience surgery due to leiomyomas. In addition, the data analysis allowed us to determine which factors contribute significantly to the risk of surgery due to this disease. Our results show that increased age among premenopausal women may be a risk factor for UL. This finding is not surprising, since several epidemiologic studies have found that prevalence of fibroids during the reproductive years increase with age [22,23]. Based on our model, at age 20 the probability of surgery for women with normal weight is under 5%, and by age 50 this probability increases to over 20%, which shows a continuous and significant effect.

Early [24-26] and late [27,28] studies have found an association between elevated body mass index and higher incidence of uterine leiomyomas in African-American, Caucasian and Asian populations. In a study from Boston, Massachusetts, a half of the hysterectomy -or myomectomy- confirmed patients with leiomyomata were overweight, and 16% were severely obese [24]. In our study, one third of women operated because UL were overweight and the fifth part was obese, percentages significantly higher than those observed in the control group. In our model and for women 40 years old, the probability of needing surgery is nearly 50 percent for overweight women and 60 percent if they are obese. This finding could be particularly important in the Canary Islands, a population that exhibit one of the highest excess weight rates in Spain, with nearly one third of women overweight and one fifth obese [29]. Therefore, leiomyomas requiring surgery could be another comorbid disease state associated with overweight and obesity, a relationship that have been established for symptomatic uterine fibroids and obesity [24,28].

The peripheral conversion of androgens to estrogens that occurs in fat is unlikely to explain an association between BMI and UL because the vast majority of circulating estrogen in premenopausal women is from the ovaries [23]. However, BMI is inversely correlated with circulating levels of sex hormone binding globulin, so circulating estrogen and androgen may be more bioavalaible in heavy compared with light women [23]. Moreover, in obese premenopausal women, decreased metabolism of estradiol by the 2-hydroxylation route reduces the conversion of estradiol to inactive metabolites, which could result in a relatively hyperestrogenic state [30]. Finally, it cannot be discarded that other adipose tissue-derived proteins, such as leptin and adiponectin, acting individually or in concert with estrogens may influence tumor development [31]. Evidence about a role of these peptides in breast cancer cell lines is becoming increasingly manifest [31-33]. In addition, leptin stimulates the growth of an ovarian cancer cell line, an effect that is partially mediated by ER transcriptional activation via the STAT-3 signaling pathways [34]. In leiomyomas, it has been suggested that leptin, acting through autocrine-paracrine mechanism(s), may be involved in the development of uterine myomas [35].

Until now, the relationship between oral contraceptive use and the risk of leiomyomas has showed inconsistent associations [22,23], with studies showing positive [36], inverse [21,37] and no association [27,38]. In addition, two studies found and increased risk of developing leiomyomas only when oral contraception stars early in life [15,39]. It has been previously suggested that because women with fibroid may take oral contraceptives to control their symptoms (menstrual bleeding), a positive association could arise, especially in case-control studies of surgical fibroid cases [23]. In our sample, the frequency of women using contraceptive pills in both groups was very similar, being, about a fifth. However, the duration of the contraceptive use was clearly different, much

greater for the cases. According logistic modeling after 12 consecutive months of contraception use the probability of surgery for 40 years old women with leiomyoma under normal weight raise to two-thirds and is nearly 100% in case she is overweight or obese. This scenario is practically the same to that found for women that have been subject to long-cycle in vitro fertilization treatment. These data strongly support the idea that exogenously administered sexual hormone contributes significantly to development of leiomyomas.

Parity has been inversely associated with fibroid risk in earlier and late studies [23,40]. It has been suggested that this association is attributable to a protective effect of postpartum involution of the uterus, so after each pregnancy the uterus rapidly returns to prepregnancy size by dramatic remodeling of the tissue and small fibroids are eliminated during this process [40]. However, in our study, the frequency of women who have undergone surgery because of fibroids and with two or more children was almost twice higher than the control group. In addition, a slightly increase of nulliparous was observed in the control group.

Logistic analysis has no retained parity as a factor associated with the surgery for women with fibroids. In previous studies, parity was not inversely associated with risk of hysterectomy-confirmed uterine leiomyomata [15,39]. It has been proposed that women with uterine leiomyomas who had completed childbearing are more prone to undergone hysterectomy than women with leiomyomas who had not finished childbearing, and hence risk estimates might be biased [39]. Alternatively, age at childbearing is a critical factor, since pregnancies early in the reproductive years may occurs before the formation of myomas, or when tumors are still small, while late pregnancies may occur when myomas are too large to regress [3]. Therefore, in those women with pre-existing fibroids, the uterus remodeling after delivery may not remove them, and accumulation of hormones in each pregnancy could even contribute to their growth which ultimately leads to surgical removal. This may explain the trend toward a positive association between parity and risk of surgery for women with leiomyoma observed in this study and previous one [3]. Interestingly, the average age of Spanish women having their first child have been continuously increasing from 28 years in 1975 to 30 years in 1995 and 31,06 years in 2011, which add support to this hypothesis [41].

Our study is affected by some limitations. The first limitation is based on the retrospective character of the study that may be affected by errors in medical records and clinical laboratory reports. This problem may lead to selection, information and misclassification bias that is impossible to identify and quantify. On the other hand, the study is affected by a lack of generalizability of results to other patients populations due to the sample was obtained from the Canary Islands, a population that exhibit one of the highest excess weight rates in Spain, and weight was a central factor found for increase the risk of surgery because leiomyomas . Considering the limitations and potential sources of bias above exposed, according to our results, and knowing that sex hormones are essential for the development of fibroids, we propose that factors such as age increase, prolonged contraceptive use, IVF treatments, overweight and obesity, lead to a higher and more prolonged exposure of the uterus to steroid hormones. This effect could be cumulative, leading to increased risk of growth of already existing fibroid or the formation of new ones in those uteri at risk of developing leiomyomas. The sum of all these cumulative effects over 20-30 years contributes very significantly to increase the risk of surgery for fibroids.

References

1. Walker CL, Stewart E A (2005) Uterine fibroids: the elephant in the room. Science 308: 1589-1592.
2. Evans P, Brunsell S (2007) Uterine fibroid tumors: diagnosis and treatment. Am Fam Physician 75: 1503-1508.
3. Parker WH (2007) Etiology, symptomatology and diagnosis of uterine myomas. Fertil Steril 87: 725-736.
4. Sankaran S, Manyonda IT (2008) Medical management of fibroids. Best Pract Res Clin Obstet Gynaecol 22: 655-76.
5. Coronado GD, Marshall LM, Schwartz SM (2000) Complications in pregnancy, labor, and delivery with uterine leiomyomas: a population-based study. Obstet Gynecol 95: 764-769.
6. Rein MS, Nowak RA (1992) Biology of uterine myomas and myometrium in vitro. Semin Reprod Endocrinol 10: 310-319.
7. Flynn M, Jamison M, Datta S, Myers E (2006) Health care resource use for uterine fibroid tumors in the United States. Am J Obstet Gynecol 195: 955-964.
8. Hodge JC, Morton CC (2007) Genetic heterogeneity among uterine leiomyomata: insights into malignant progression. Hum Mol Genet 16: 7-13.
9. Rein MS, Powell WL, Walters FC, Weremowicz S, Cantor RM, et al. (1998) Cytogenetic abnormalities in uterine myomas are associated with myoma size. Mol Hum Reprod 4: 83-86.
10. Ligon AH, Morton CC (2001) Leiomyomata: heritability and cytogenetic studies. Hum Reprod Update 7: 8-14.
11. Li S, Mc Lachlan JA (2001) Estrogen-associated genes in uterine leiomyoma. Ann NY Acad Sci 948: 112–120.
12. Li S, Chiang TC, Richard-Davis G, Barrett JC, Mclachlan JA (2003) DNA hypomethylation and imbalanced expression of DNA methyltransferases (DNMT1, 3A, and 3B) in human uterine leiomyoma. Gynecol Oncol 90: 123-130.
13. Maruo T, Ohara N, Wang J, Matsuo H (2004) Sex 292 steroidal regulation of uterine leiomyoma growth and apoptosis. Hum Reprod Update 10: 207-220.
14. Marshall LM, Spiegelman D, Barbieri RL, Goldman MB, Manson JE et al. (1997) Variation in the incidence of uterine leiomyoma among premenopausal women by age and race. Obstet Gynecol 90: 967-973.

15. Marshall LM, Spiegelman D, Goldman MB, Goldman MB, Manson JE et al. (1998) A prospective study of reproductive factors and oral contraceptive use in relation to the risk of uterine leiomyomata. Fertil Steril 70: 432-429.

16. Stewart EA (2001) Uterine Fibroids. Lancet 357: 293-298.

17. Okolo S (2008) Incidence, aetiology and epidemiology of uterine fibroids. Best Pract Res Clin Obstet Gynaecol 22: 571-588.

18. Xu Q, Takekida S, Ohara N, Chen W, Sitruk-Ware R, et al. (2005) Progesterone receptor modulator CDB-2914 down-regulates proliferative cell nuclear antigen and Bcl-2 protein expression and up-regulates caspase-3 and poly(adenosine 5'-diphosphate-ribose) polymerase expression in cultured human uterine leiomyoma cells. J Clin Endocrinol Metab 90: 953-961.

19. Yin P, Lin Z, Cheng YH, et al. (2007) Progesterone receptor regulates Bcl-2 gene expression through direct binding to its promoter region in uterine leiomyoma cells. J Clin Endocrinol Metab 92: 4459-4466.

20. Fernandez H, Farrugia M, Jones SE, Mauskopf JA, Oppelt P, et al. (2009) Rate, type, and cost of invasive interventions for uterine myomas in Germany, France, and England. J Minim Invasive Gynecol 16: 40-46.

21. Faerstein E, Szklo M, Rosensheim N (2001) Risk factors for uterine leiomyoma: a practice-based case-control study. I. African-American heritage, reproductive history, body size, and smoking. Am J Epidemiol 153: 1-10.

22. Flake GP, Andersen J, Dixon D. (2003) Etiology and pathogenesis of uterine leiomyomas: a review. Environ Health Perspect 111: 1037-1054.

23. Laughlin SK, Schroeder JC, Baird DD (2010) New directions in the epidemiology of uterine fibroids. Semin Reprod Med 28: 204-217.

24. Shikora SA, Niloff JM, Bistrian BR, Forse RA, Blackburn GL (1991) 318 Relationship between obesity and uterine leiomyomata. Nutrition 7: 251-255.

25. Lumbiganon P, Rugpao S, Phandhu-fung S, Laopaiboon M, Vudhikamraksa N, et al. (1996) Protective effect of depot-medroxyprogesterone acetate on surgically treated uterine leiomyomas: a multicentre case-control study. Br J Obstet Gynaecol 103: 909-914.

26. Sato F, Nishi M, Kudo R, Miyake H (1998) Body fat distribution and uterine leiomyomas. J Epidemiol 8: 176-180.

27. Parazzini F, Chiaffarino F, Polverino G, Chiantera V, Surace M, et al. (2004) Uterine fibroids risk and history of selected medical conditions linked with female hormones. Eur J Epidemiol 19: 249-253.

28. Takeda T, Sakata M, Isobe A, Miyake A, Nishimoto F et al. (2008) Relationship between metabolic syndrome and uterine leiomyomas: a case-control study. Gynecol Obstet Invest 66: 14-17.

29. Serrano-Aguilar P, Munoz SR Navarro, Ramallo-Fariña Y, Trujillo-Martin MM (2009) Obesity and health related quality of life in the general adult population of the Canary Islands. Qual Life Res 18: 171-177.

30. Schneider J, Bradlow HL, Strain G, Levin J, Anderson K, et al. (1983) Effects of obesity on estradiol metabolism: decreased formation of nonuterotropic metabolites. J Clin Endocrinol Metab 56: 973-978.

31. Cleary MP, Grossmann ME (2009) Minireview: Obesity and breast cancer: the estrogen connection. Endocrinology 150: 2537-2542.

32. Fusco R, Galgani M, Procaccini C, Franco R, Pirozzi G, et al. (2010) Cellular and molecular crosstalk between leptin receptor and estrogen receptor alpha in breast cancer: molecular basis for a novel therapeutic setting. Endocr Relat Cancer 17: 373-382.

33. Yu Wei, GU Jun-chao, LIU Jian-zhong, Wang SH, Wang Y et al. (2010) Regulation of estrogen receptors alpha and beta in human breast carcinoma by exogenous leptin in nude mouse xenograft model. Chinese Med J 123: 337-343.

34. Choi JH, Lee KT, Leung PC (2011) Estrogen receptor alpha pathway is involved in leptin-induced ovarían cancer cell growth. Carcinogenesis 3: 589-596.

35. Markowska A, Belloni AS, Rucinski M, Parenti AR, Nardelli GB et al. (2005) Leptin and leptin receptor expression in the myometrium and uterine myomas: Is leptin involved in tumor development? Int J Oncol 27: 1505-1509.

36. Ramcharan S, Pellegrin FA, Ray RM, Hsu JP (1980) The Walnut Creek Contraceptive Drug Study. A prospective study of the side effects of oral contraceptives. J Reprod Med 25: 345-372.

37. Chiaffarino F, Parazzini F, La Vecchia C, Marsico S, Surace M, et al (1999) Use of oral contraceptives and uterine fibroids: results from a case-control study. Br J Obstet Gynaecol 106: 857-860.

38. Samadi AR, Lee NC, Flanders WD, Boring JR 3rd, Parris EB (1996) Risk factors for self-reported uterine fibroids: a case-control study. Am J Public Health 86: 858-862.

39. Wise LA, Palmer JR, Harlow BL, Spiegelman D, Stewart EA, et al. (2004) Reproductive factors, hormonal contraception, and risk of uterine leiomyomata in African-American women: a prospective study. Am J Epidemiol 159: 113-123.

40. Baird DD, Dunson DB (2003) Why is parity protective for uterine fibroids? Epidemiology 14: 247-250.

41. Bosch X (1998) Investigating the reasons for Spain's falling birth rate. Lancet 352: 887.