UNNECESSARY CONFUSION ABOUT FAMILY PLANNING AFTER INTRAHEPATIC CHOLESTASIS OF PREGNANCY

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Raskaushepatoosin epäillään johtuvan maksa kyvyttömyydestä sietää loppuraskauden hormonitaakkaa, minkä vuoksi estrogeeniä sisältävät ehkäisymenetelmät ovat aiemmin olleet vasta-aiheisia hepatoosin sairastaneille. Tutkimuksen tavoitteena oli selvittää, miten tällaiset rajoitteet ovat vaikuttaneet näiden naisten perhesuunnitteluun ja eri ehkäisymenetelmien käyttöön.

Tutkimuksessa kartoitettiin kyselylomakkeella ehkäisyyn, raskauteen, synnytykseen ja seksielämään liittyviä seikkoja raskaushepatoosin sairastaneilta naisilta ja heidän verrokeiltaan, jotka ovat kaikki synnyttäneet Tampereen yliopistollisessa sairaalassa vuosina 1969–1988. Kysely toteutettiin postitse vuonna 2010. Aineistoa käsiteltiin tilastollisesti SPSS 16.0 -ohjelmalla.

Raskaushepatoosin sairastaneet ovat rajoittaneet verrokkeja useammin lapsilukuaan terveydellisistä syistä. Heidän perheissään on myös verrokkeja useammin vain yksi lapsi. Yhdistelmäehkäisypillereiden käyttö on merkitsevästi harvinaisempaa hepatoosin sairastaneiden keskuudessa verrokkeihin nähden. Synnytykset ovat molemmissa ryhmissä olleet yhtä onnistuneita.

On tärkeää, että lääkärit tarjoavat potilaille tarkkaa ja ajanmukaista tietoa raskaushepatoosista ja sen vaikutuksista. Potilaita tulisi ohjeistaa ehkäisyn eri mahdollisuuksista ja tarjota heille sopivia vaihtoehtoja. Myös hyvä vuorovaikutus ja potilas-lääkäri -suhde auttavat vähentämään turhaa pelkoa ja huolta uuden raskauden ja perhesuunnittelun suhteen.

Olen artikkelin ensimmäisenä kirjoittajana tehnyt aiheeseen liittyviä kirjallisuushakuja, jäsennellyt taulukoitua aineistoa, suorittanut tilastolliset testiajot SPSS-ohjelmalla sekä kirjoittanut artikkelin raakaversiot itsenäisesti tutkimusryhmän tuella. Olen myös yhdessä tutkimusryhmän kanssa muokannut artikkelia viimeisimpään submittointiin asti. Artikkeli on hyväksytty julkaistavaksi Contraception-lehdessä.

SISÄLLYS

Unnecessary confusion about family planning after intrahepatic cholestasis of pregnancy

Anni Mölsä, Kaisa Turunen, Kari J. Mattila, Markku Sumanen

Abstract

Background: As conceptions have changed regarding the suitability of oral contraceptives for women with a history of intrahepatic cholestatis of pregnancy (ICP), we studied whether the contraindications formerly in force had affected family planning decisions and mode of contraception among women with such a history.

Study design: ICP women and their controls who gave birth in 1969-1988 in Tampere University Hospital, Finland, were sent a questionnaire in 2010. The inquiry covered items concerning contraception, deliveries, menstruation and sex life.

Results: ICP women had limited their number of children for health reasons more often than the controls. They also more often had a single child compared to the controls. The use of oral contraceptives was less common among ICP women. Deliveries were equally successful in both groups.

Conclusion: Physicians should provide sufficient and accurate information on ICP to the patients. Proper introduction of suitable contraception methods and successful communication with the patients would also reduce unnecessary problems and confusion regarding future family planning practices.

Introduction

Intrahepatic cholestasis of pregnancy (ICP) usually manifests in the third trimester as skin itching especially on the palms and soles and as an elevation of serum levels of bile acids and liver enzymes (1,2). The incidence of ICP in Finland is 0.54-1.5% of pregnancies (3-5), which is the same as that in Europe on average (2). ICP may recur in 40-50% of subsequent pregnancies (1,6). In almost one fifth of cases ICP is familial, and in such cases recurs in 92 % of subsequent pregnancies (7).

ICP is thought to be the result of insufficient liver capacity to metabolize high amounts of placental hormones during pregnancy (1,6). The ultimate cause of the condition remains unknown but is thought to be multifactorial: genetic, hormonal and environmental. The severity of ICP varies in subsequent pregnancies (1). More severe cases occur in winter (1), and nutritional factors, for example selenium deficiency, may have a role in the etiology (8-10).

ICP has no major physical consequences except for higher frequencies of cesarean sections and inductions (5,11). Itching may be intensive and disturbing but fades quickly postpartum. Some liver and biliary diseases seem to be more frequent among women with a history of ICP (12). For the fetus consequences may be more severe: ICP increases the risk of preterm birth (13), fetal distress during labor (3,13) and intrauterine death (3).

Oral contraceptives (OCs) were first introduced in the United States in 1960 and in Finland two years later (14,15). The first-generation pills contained a 150µg estrogen component and 9,85mg of progestogen, but by 1970 the amount of estrogen was reduced to 50µg on account of reported thromboembolic cases (16). In 1974, low-dose OCs (containing 20-35µg of estrogen) were released - also in Finland, and in the same year the former high-dose pills were withdrawn from the market (16,17). Progestin-only OCs were first available in Finland in 1971 and copper-releasing intrauterine devices (IUDs) in 1972 (17).

Sexual behavior became more liberal (18,19) and the use of different contraceptive methods changed rapidly during the 1970s and 1980s, partly due to the new contraceptives introduced (20). Whereas in the early 1970s the most popular contraception methods in Finland were the condom, OCs and withdrawal, by the end of the 1980s IUDs had become the method most used (20). IUDs were the most popular method especially among married women, whereas younger women preferred OCs (20). Since 1982, the pill has been gaining in popularity among all Finnish women (20,21).

Cholestatic states during use of OCs have been reported in women who have developed ICP (22-24). As the incapacity of the liver to metabolize the increased load of estrogen during pregnancy has been held to be implicated in ICP pathogenesis, it is possible that by the same mechanism the OCs can cause cholestasis (1,25). Hence, oral contraceptives have been contraindicated or at least not advocated for women with a history of ICP (25,26). According to a French study from 1997, low-dose OCs can be prescribed to ICP women once their liver function test results have normalized since OCs did not cause pruritus or major rise in liver function tests for most ICP women (24). Check-ups including liver function tests and providing information about the risk of cholestasis are still recommended (2). However, contradiction between different viewpoints still occurs.

As the use of estrogen-containing contraceptives was formerly contraindicated after an ICP pregnancy, we here studied the contraceptive practices of ICP women and any complications they might have experienced regarding their choices. We also sought to establish whether ICP had affected women's attitudes towards their sex life, and the possible impact of this on their family planning practices.

Material and Methods

The focus in this study was on women who had developed ICP when giving birth in Tampere University Hospital in the period 1969-1988. Altogether 575 women were diagnosed (11) as having ICP during that period. We selected two controls for each of their deliveries (687) from the hospital's labor register, chronologically the previous and

the next parturient without ICP. In the autumn of 2010 we conducted a postal inquiry among the ICP patients and the controls. Addresses were obtained from the Population Register Centre in Finland. We sent the questionnaire to 1 779 women with one reminder and received 1 178 acceptable responses. The flow chart of the study population is shown in Figure 1.

For the demographic characteristics of the study population we considered age, educational level and body mass index (BMI). Ages were expressed in full years on the last day of 2010. Education was described by two classes, high, referring to those with the matriculation examination (Finnish equivalent of UK A-levels) and low indicating education below this. BMI was calculated from the reported weight (kilograms) and height (meters) and then classified into three categories: normal (BMI <25.0), overweight (BMI 25.0-29.9) and obese (BMI ≥30.0).

The questionnaire consisted of 85 items covering the following main aspects: health in general, symptoms and complaints, diseases or conditions diagnosed by a doctor, health habits and gyneco-obstetric history. The questionnaire was identical for the ICP women and the controls. The participants did not know the exact reason (history of ICP) for being selected to this study.

The questions dealt with contraception, sexual health, pregnancies and menstruation. Respondents were asked whether they had used contraception and if so, which method; they selected one or more of the 15 alternatives offered. We also inquired after problems concerning contraception: a disease or side-effect which had prevented the use of oral contraceptives (OCs), injurious effects which had led to the removal of an intrauterine device, rubber latex allergy, failure of the contraceptive method used, disagreement with partner over contraceptive method, or any “other problems they might have encountered”. The questionnaire included a list of possible adverse effects OCs may have caused: rise in liver function test levels, rise in blood pressure, weight gain, depression or other mental symptoms, reduced sexual drive, migraine, blood clot (referring to embolus or thrombosis), acne or “other”. Respondents were also asked if they or their partners had

been sterilized and whether they had had a hysterectomy. They were also asked whether they had been told that they could not use OCs or hormonal treatment in the future on account of a liver problem, and if they had had any type of disease or had experienced any symptom during pregnancy which prevented them from using hormones.

Pregnancy and family planning-related questions concerned the lifelong number of pregnancies (also twin or triplet pregnancies), deliveries and children alive, the number of miscarriages, abortions and cesarean sections. The number of deliveries was classified into three categories: one delivery, two deliveries and three or more deliveries. We also asked whether the respondents had limited their number of children for health reasons or had had specific problems during pregnancy (rise in blood pressure, proteinuria, itching with rise in liver function test results, rise in blood sugar, urinary tract infections or blood clots). To establish the menstrual history, we asked the age at menarche and, if relevant, menopause.

The questions related to sexuality and relationship encompassed the following: "How important is sex to you? "How satisfied are you with your sex life?" and "How satisfied are you with your current domestic partnership/marriage/relationship?" There were seven categories on a Likert type scale; 1 indicating not at all important/very dissatisfied and 7 very important/very satisfied. The categories were divided into two classes for purposes of analysis: important/satisfied (categories 5-7) and not important/dissatisfied (1-4).

The data were analyzed with SPSS 16.0 for Windows. The results were presented as frequencies. Statistical significance was tested by chi-square test.

Results

There were no statistically significant differences between the ICP group and controls in any demographic variable (age, educational level and BMI) (Table 1).

Contraception

There was a statistically significant difference in the use of combined oral contraceptives (OCs), ICP patients having used this mode less than the controls (52.0% vs. 62.9%, $p<0.001$). Otherwise the use of the various methods did not differ between the two groups. Compared with the controls, there was a trend to use more progestin-only pills among the ICP patients (20.8% vs. 16.1%, $p=0.052$) (Table 2). Sterilizations were equally common in both groups (32.3% vs. 31.4%, $p=0.733$).

In general, there were no notable differences in the number of contraceptive complications (40.8% vs.36.6%, $p=0.174$). Causes for complications, however, varied between the groups. The ICP patients had more often had a disease preventing the use of OCs whereas the controls had disagreed with their partners over the method used more often than the ICP women. Otherwise frequencies of causes of problems were similar (Table 3).

The adverse effects of oral contraceptives are shown in Table 4. More subjects had elevated liver function tests than controls (31.1% vs. 5.7%, $p<0.001$). Other adverse effects did not differ statistically significantly between the groups.

In the ICP group, 27.5% of the women had had a disease or a symptom during pregnancy which subsequently prevented the use of oral contraceptives. In the control group, the proportion was 2.2%, the difference being statistically significant ($p< 0.001$). The reported diseases and symptoms were almost merely rises in liver function tests or itching in the ICP group whereas controls mentioned sporadic cases of hypertension, migraine, diabetes, preeclampsia, epilepsy and embolus. Of the ICP women, 40.7% as opposed to 2.2% of the control group had been told that they could not use OCs due to their liver complication ($p< 0.001$).

Deliveries

Cesarean sections and multiple pregnancies occurred more often among the ICP patients, and the differences were significant. There were no specific differences between the groups in figures for abortions, miscarriages or ectopic pregnancies. The ICP women had

limited their number of children for health reasons notably more frequently than the controls, the significance being less than 0.001 (Table 5). There was a statistically significant difference (p=0.001) in the classified number of deliveries: compared with controls ICP women had had fewer children. They had finished their families more often after just one child (Figure 2).

Menstruation

There was a slight difference between the ICP women and the controls in age at menarche, but this was not statistically significant, nor was the difference in age at menopause. There were no differences in the number of hysterectomies between the two groups.

Sexuality and relationship

Significantly more ICP patients than controls considered sex not important, the difference being 7.6 percentage units (p=0.022). There were no statistically significant differences in ratings of satisfaction with sex life and current relationship (p=0.355 and p=0.543).

Discussion

The results reveal the ICP patients to have limited the number of their children for health reasons more often than the controls. They also more often had just one child in their families.

ICP would appear to be the reason for not having more children. In fact, however, many previous studies have shown that ICP does not markedly affect the outcome of pregnancy (11) and that ICP should not be a contraindication for future pregnancies (26). ICP does not automatically recur or be more severe in subsequent pregnancies and the risks for the fetus are minor in well-organized follow-up (5,11). Our findings likewise show pregnancies to be equally successful in both groups; there were no significant differences in numbers of abortions, miscarriages and ectopic pregnancies. On the other hand, ICP

was associated with an increased incidence of cesarean sections and inductions (5,11), which mothers may experience as frightening and uncomfortable situations. The symptoms of ICP can also be extremely disturbing, especially at night. The condition might have aroused uncertainty or fear for the baby's well-being, especially if communication with the doctor had been insufficient and details of ICP not fully clear to the patient. Negative experiences of pregnancy and child-birth may diminish the desire to have more children.

In Finland, all women visit maternity clinics in primary health care several times during their pregnancies (27). Liver function tests are taken if itching appears. If the tests are elevated, the mother will be referred to an obstetric clinic in secondary care for more detailed follow-up.

The body of data here was substantial (1 178 respondents) and the response rate (66%) for the questionnaire exceptionally good. The data can be regarded as a reliable and representative cross-section of Finnish women, since all ICP patients giving birth in Tampere University Hospital in 1969-1988 were included and the number of controls was twice that of ICP cases.

The data were collected by a questionnaire which the participants filled in at home several years after the event. It is possible that some sections of the questionnaire were unclear, with the result that the respondents did not fully understand what was being inquired after. It is also probable that a number of respondents were unable to remember particular details regarding matters arising several decades ago. Also the conceptions, beliefs and assumptions of the participants may have affected their answers and rendered them medically imprecise. The respondents did not know they were selected to this study owing to their ICP history. Therefore, we do not know whether their answers concern the index pregnancy selected from the hospital's labor register or their other possible pregnancies. Hence, we have to consider the answers as a lifelong process.

Since the period covered in this study was fairly long, courses of action and guidelines for treatment may conceivably have differed from each other and from those currently applied, for example in the diagnostics of ICP, the follow-up of pregnancy or the prescription of oral contraceptives.

The findings here show that oral contraceptives have raised liver function test results in women who have suffered from cholestasis of pregnancy. Some older studies have arrived at similar conclusions in the context of high-dose estrogen (22,23) but only a few have addressed the consequences of the low estrogen dose pills used today (24,28). The majority of guidelines concerning the prescription of OCs are thus based on studies which are possibly outdated. It is probable that ICP women's liver values have been tested more often than the controls' because of their background with cholestasis. This might have increased the number of elevated but harmless liver function test results. In Finland, according to the Evidence-Based Medicine Guidelines (29), an active hepatic disease is a contraindication for prescribing OCs. However, for some reason a previous history of ICP has also been placed in the same category as active hepatic disease. Moreover there are also discrepancies between textbooks of different specialties: according to one Finnish textbook of gynecology and obstetrics (30) OCs can be prescribed to women with an ICP history, while the textbook of hepatology (31) considers ICP a contraindication.

It emerged here that ICP patients had used OCs less than the controls, most likely because they had been told that a liver complication or symptom during pregnancy prevented their use. It is not certain whether they really had been told this or whether it was merely a conclusion they themselves had drawn, thus abandoning even a trial of the pills. It is possible that the pills caused more symptoms to the ICP women before the year 1974 when low-dose OCs were first introduced in Finland. This might have caused hesitation to provide oral contraceptives to ICP patients. Altogether 48% of the ICP patients here had never tried OCs. This might explain the differences seen in disagreement with their partner over contraceptive method and appreciation of sex. Since the range of alternatives had been restricted for health reasons from ICP women it may have been easier for the couples to settle for the remaining options. On the other hand,

difficulties and frustration may have arisen about sex, as possibly the most desired option (OCs) had not been available, this leading to undervaluation of sex.

Even though the OC users of the ICP group had had raised liver function tests, the respondents did not, however, report any serious complications. We hence agree with current international recommendations that women with a history of ICP can use OCs provided that their liver function tests are followed.

Doctors exert an influence on their patients, and even isolated random comments may leave a lasting impression and form a permanent notion for them. It would thus be extremely important for doctors in primary health care or those who otherwise take care of ICP patients to acquire adequate and especially accurate information regarding ICP and its consequences. It would also be important for them to pass on this information in a comprehensible way to ICP patients when consulting them about family planning and choices of contraception. Thus unnecessary problems, confusion and restrictions to family size could be prevented.

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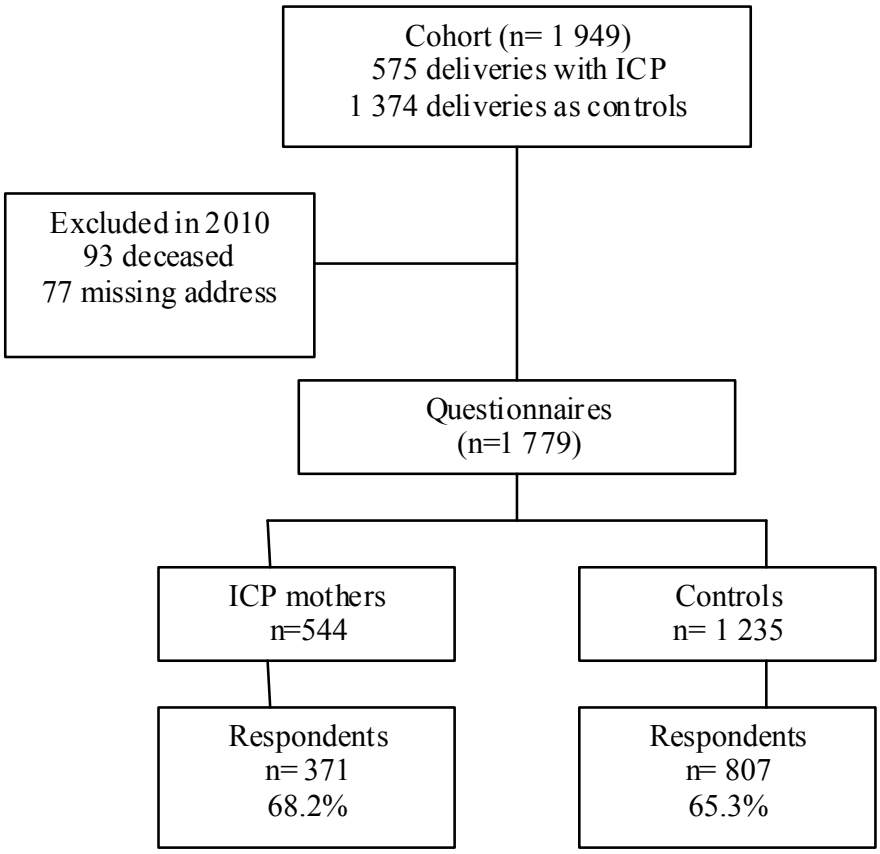

Figure 1 Flow chart of the survey population.

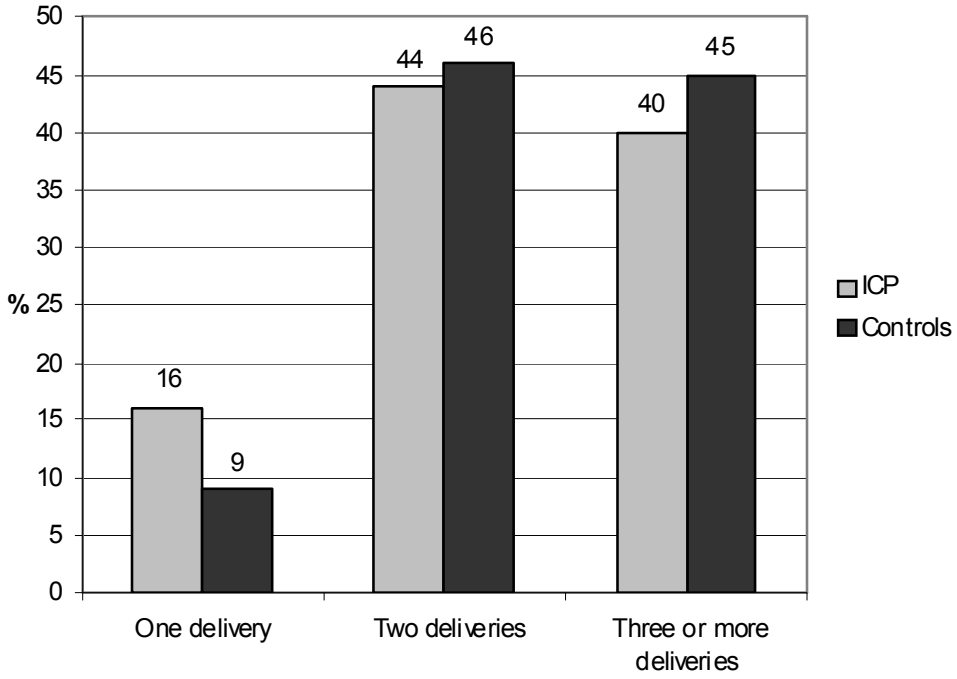

Figure 2. Number of lifelong deliveries among the ICP and control group women (p-value 0,003).

Table 1 Characteristics of the respondents in the ICP and control groups.

	ICP Group (n= 371)	Controls (n = 807)	Difference	
	%	%	% units	Significance p
Age (years)				0.742
40-49	8.6	7.8	0.8	
50-59	45.3	48.9	-3.6	
60-69	42.0	39.0	3.0	
70-89	4.0	4.1	-0.1	
Education				0.961
Low	67.0	67.2	-0.2	
High	33.0	32.8	0.2	
Body Mass Index (kg/m^2)				0.265
BMI <25.0	40.0	38.3	1.7	
BMI 25.0-29.9	33.7	38.4	-4.7	
BMI =30.0	26.3	23.3	3.0	

Table 2 Contraceptive methods used by the ICP and control group women.

	ICP patients n=371 %	Controls n=807 %	Difference % units	Significance p
Progestin-only pill	20.8	16.1	4.7	0.052
Condom	68.7	66.5	2.2	0.457
Interrupted intercourse	16.2	15.1	1.1	0.642
Copper-releasing IUD	61.5	60.5	1.0	0.748
Contraceptive patch	1.1	0.4	0.7	0.143
Spermicide	7.5	6.8	0.7	0.648
Emergency contraception, IUD	0.0	0.1	-0.1	0.498
Other contraception	0.5	0.7	-0.2	0.692
Vaginal ring	0.0	0.2	-0.2	0.337
Diaphragm	0.3	0.6	-0.3	0.433
Subdermal contraceptive implant	1.1	1.9	-0.8	0.323
Rhythm method	5.9	6.9	-1.0	0.518
Emergency contraception, pills	0.8	2.1	-1.3	0.109
Progestin-releasing IUD	26.4	28.9	-2.5	0.383
Contraceptive pill	52.0	62.9	-10.9	<0.001
No method used	4.9	5.3	-0.4	0.732

Table 3 Problems with contraceptive methods in the ICP and control groups.

	ICP patients	Controls	Difference	
	n=371 %	n=807 %	% units	Significance p
Disease or symptom during pregnancy preventing later use of OCs	27.5	2.2	25.3	<0.001
Disease or side-effect preventing the use of OCs	26.1	11.5	14.6	<0.001
Disagreement with partner over contraceptive method	0.3	1.6	-1.3	0.048
Other problems	1.3	3.0	-1.7	0.094
Failure of the method	11.3	13.5	-2.2	0.297

Table 4 Adverse effects of oral contraceptives in the ICP and control groups among those having used OCs.

	ICP patients	Controls	Difference	
	n=193 %	n=508 %	% units	Significance p
Rise in liver function test results	31.1	5.7	25.4	<0.001
Migraine	10.9	8.3	2.6	0.280
Other problems	6.7	6.7	0.0	0.984
Embolism	1.0	1.6	-0.6	0.591
Depression or other changes in mood	15.0	16.3	-1.3	0.672
Rise in blood pressure	3.1	4.7	-1.6	0.345
Weight gain	26.4	28.0	-1.6	0.686
Acne	0.5	2.4	-1.9	0.106
Decrease in sexual desire	7.3	11.4	-4.1	0.105

Table 5 Obstetric characteristics of the ICP and control group women.

Obstetrics	ICP patients (n=371) %	Controls (n=807) %	Difference % units	Significance p
Restriction of number of children for health reasons	17.3	7.7	9.6	<0.001
Cesarean sections	21.8	15.5	6.3	0.008
Twin or triplet pregnancies	6.5	3.2	3.3	0.010
Abortions	25.1	21.8	3.3	0.216
Ectopic pregnancies	6.7	5.5	1.2	0.383
Miscarriages	24.8	26.0	-1.2	0.655