Chapter 11

Contraceptive Methods and the Subsequent Search for a Pregnancy

Blanca Patricia Bautista Balbás,
Luis Alfredo Bautista Balbás and Alicia Pouso Rivera

Additional information is available at the end of the chapter

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Abstract

Many women are concerned about their future fertility, about pregnancy complications and about the health of their future child when choosing a contraceptive method and sometimes women want to interrupt the contraception – maybe after years of use – in order to attempt pregnancy. Return to fertility, has been thoroughly analyzed in the literature. This chapter provides evidence-based information and discusses the potential doubts of women. Return to fertility has been consistently found to be sure, albeit sometimes slightly slow in the short term: pregnancy rates after 1 year of contraceptive interruption are 79–95% for oral contraceptives, 79–96% for levonorgestrel IUD, 71–91% for copper IUDs, around 80% for implants and 75–80% for injectable contraceptives. About 50% women are pregnant 3–6 months after contraceptive discontinuation; around 90–95% of women had achieved pregnancy 2 years after stopping their contraceptive method. Some studies have found associated risks of fetal malformations when women take oral contraceptive pills *after* conception (though other studies disputed these results). However the offspring of women who used oral contraceptives *before* conception does not show an increased risk of fetal death, miscarriage, gestational hypertension, major newborn structural defects or hypospadias. The effect on birth weight seems small and inconclusive.

Keywords: return to fertility, contraceptive, UID, copper, pill, contraceptive implant, hormonal contraceptive, injectable, depot, pregnancy rate

1. Introduction

Contraceptive methods are the instrument that women use to control their fertility at any given time in their lives so that the pregnancy would be produced by choice and not by

chance. In any case, women's reproductive goals change at any moment of the woman's fertile life; this is why the reversibility of the chosen method is especially important for them [1].

For many authors, infertility refers to the inability of a couple to conceive after having 12 months of regular sexual intercourse without using any contraceptive method; some authors emphasize intercourse "in the fertile phase of the menstrual cycles" [2]. Infertility rate is better estimated by prospective studies; around 80% women become pregnant in the first cycles and approximately, 85–90% couples will conceive within 1 year if they have regular unprotected sex. 50% of couples who did not manage to conceive after 12 months (infertility definition) will manage to conceive spontaneously in the next 36 months; after this time point spontaneous conception in infertile couples is considered only sporadic [2]. Infertility (both male and female) is influenced by many reproductive or lifestyle factors. Physical causes of female infertility include alterations in ovulation and abnormal functioning or structures of reproductive organs, as well as age and lifestyle-related risk factors: alcohol or drug use, obesity, tobacco habit, exposure to a range of environmental toxins, etc. [3, 4] Consequently, studies assessing pregnancy rates or time to pregnancy following cessation of contraceptive use may be influenced by many underlying factors specific to the population under study.

Future pregnancy complications and pregnancy outcome is another important concerning issue of women who want to become pregnant; these events can happen in any pregnancy. Spontaneous abortion is one of the most common pregnancy complications; abortion rates are especially high in the weeks [5]. 14% of pregnancies end with fetal loss, with rates varying between 9% and 75% or more depending on the age, population and other factors [6, 7]. Ectopic pregnancy incidence rates vary between 1 and 2% of live births in developed countries, maybe reaching up to 4% in women subject to assisted reproductive treatments [8]. Preterm birth rates range from 5% of babies in European Countries to 18% in African countries [9]. Induced abortion rates also vary greatly depending in many psychosocial factors [7].

At the time of choosing a contraceptive method, women value aspects such as effectiveness, comfort, price, safety and early recovery of fertility after ceasing using this method. Past experiences with contraception and future fertility intentions also can play a role in this decision. Quite often the reversibility of the method is an important concern for women; the lack of information plus the acquisition of misconceptions about methods can increase general mistrust in long-acting contraceptive methods and lead to reduced use of these. The midwife can exert an important role solving women doubts, considering their concerns and helping them choose the most suitable contraceptive method in each case.

Male condom was the mainstay of contraception for several decades, being also immediately reversible and effective at preventing sexually transmitted diseases (STDs). **Combined Oral Contraceptive (COC) Pill**, which contains estrogens and progesterone, was first approved for contraceptive use in the United States in 1960. Combined hormonal methods also include patches and vaginal rings. Unlike combined methods, **progesterone-only** contraceptive methods are not associated with cardiovascular risk or deep-vein-thrombosis risk. These methods are monophasic and can be administered subcutaneously or orally (progesterone-only pills, POP). They lack adverse effects on lactation but cycles and menstrual bleeding become more irregular [10].

Long-acting reversible contraception methods are highly-effective reversible contraceptive methods that last for years and are easy to use. These include the intrauterine device (IUD) and

the birth control implant. The pregnancy rates in these methods are comparable to sterilization. IUD risks include uterus perforation, IUD loss, pelvic inflammatory disease, pregnancy during IUD use, etc. [11] Depot medroxyprogesterone acetate intramuscular injection (DMPA) was approved by the FDA in 1992 and became the most common injectable method in use in the USA [12]. LARC has been described to be more cost-effective than COCs, even at 1 year of use [13].

Women's preferences for anticonception have varied between different countries and generations [14, 15]. As a documented example for these variations, in the USA the Centre for Disease Control has published several periodic reports on contraception use. Apparently in the 2006–2010 report [16] a slight decrease in condom usage and an increase in intrauterine devices (IUD) was observed compared to 1995 data.

The 2011–2013 National Survey of Family Growth reported that oral contraceptives (OCs) were the most commonly used contraceptive method in the United States (16% of women aged 15–44), followed by female sterilization (15.5%), male condom (9.4%) and long-acting reversible contraceptives (7.2%). The use of sterilization declined and the use of OCs increased with greater educational level and the use of long-acting reversible contraceptives was higher among women aged 25–34 (11.1%) compared to other age groups [17].

This chapter focuses on a particular clinical situation: those women who are using a contraceptive method and want to conceive a child. These future mothers are often worried about when they will be able to conceive and about the health of the future child. With the advent of the Internet and information technologies the access to information has become less of a problem compared to the information overload [18] and the abundance of lesser quality information. Generally speaking openness of information is positive for patients, but many issues.

Some women might have heard reports of secondary effects of contraceptive methods and they might become concerned about this; on the Internet many women talk and discuss reproductive issues via women's forums or family planning forums and this might exacerbate some natural fears of mothers. In these cases it is especially important to expose medical evidence-based facts clearly: many contraceptive methods have been available for decades and there is abundant evidence and clinical experience with them. More than 150 million women around the world use the IUD [15] and clinical studies with contraceptive methods have involved thousands of patients [1]. Case reports are seen as particularly weak evidence when compared to other studies, and personal experiences shared via the Internet should not be considered a reliable source of information. For example, a former user of IUD could have a miscarriage and she could link these two circumstances; attempts to rationalize this situation are normal part of the grief and emotional healing process in many women. However miscarriages are very common (some authors have calculated a rate of >20 miscarriages/1000 women/week in the first 8 weeks [5]) and she might just be experiencing a fortuitous event.

Press and internet newspapers can act as an immediately available and quite reliable bridge between authoritative media sources and women. Reports on contraceptive methods sometimes include expert opinion and consensus statements [19]; information presented this way could be helpful for women. Media sources also usually include noteworthy journalists' opinion articles on reproductive issues [20]; in these the separation between facts and beliefs could be less clear. Experienced midwifes and doctors can also act as a reliable bridge for women with reproductive health doubts; they can provide objective evidence-based objective information and statements that can be very helpful for women.

Over the course of many decades contraceptive methods have deeply improved. Secondary effects of oral contraceptives have been detected and lower dose formulations have been developed. Many studies have assessed long-term effects of OCs on various aspects of women's health [14, 21], including their future reproductive health. In some topics conflicting evidence is available as the results and conclusions of some studies differ from others. This is not the case for contraceptive reversibility (which has consistently been observed for decades in many studies and is remarked in NICE [13] and WHO [22] guidelines, as we will discuss later), but for some rare pregnancy events (twin pregnancy, preterm birth). Obtaining contradicting results is not uncommon in clinical research and does not necessarily imply there was a flaw conducting the study [23]. Publishing these studies is not a mistake, but inadequately interpreting them could be. Conflicting and inconclusive evidence should be treated with special caution; unconfirmed results or contradictory results are not ground for evidence-based recommendations.

In this chapter we will analyze the reversibility of physiological changes, the observed fertility changes and the future pregnancy complications of several contraceptive methods: OCs (including progestin only pill and emergency contraception), injectables, implants and IUDs.

2. Oral contraceptives

2.1. Cessation

The pathway in women using OCs to return to fertility is often straightforward. The information leaflet of the particular regime often includes clear and specific instructions for women seeking discontinuation and pregnancy (which often only consist of ceasing its use). Women are often advised to wait for their menstrual period before seeking a new pregnancy because the day of the last menstrual period is useful in pregnancy date calculations. In our center, midwifes provide preconceptional counseling, which can include contraception recommendations and assessment (this applies to contraception in general). Many health issues affecting the health of the mother and the future baby can be addressed in these visits [24] and we can only recommend this practice.

2.2. Physiology

The mechanisms of action of oral contraceptives (OCs) are derived from the effect of the estrogen and the progestin in the formulation. Estrogens act by inhibiting follicular development and inhibiting hypothalamic–pituitary ovulation trigger. Progestins increase the thickness of the cervical mucus. The effects of Oral Combined Contraceptives (COCs) on endometrium vary depending on the doses, formulation and duration of use; with current commonly used lower doses contraceptives these effects include arrest of glandular proliferation, abortive secretion, stromal hyperplasia, decidualization and atrophy [25]. Intramuscular or locally administered progestins cause endometrial atrophy [26].

There is not much information on the reversibility of these changes. For example, cervical mucus can have lower scores for the first 2 months after discontinuing OCs and decreased menstrual flow was described to last for four months [27]. Some studies have linked reduced

endometrial thickness and long-term COC usage: Talukdar et al. studied the effect long-term use of combined oral contraceptives on endometrial thickness. They gathered 137 women between 30 and 45 years old subject to frozen embryo transfer cycles and determined the endometrial thickness on day 10. The group with endometrium thin than 7 mm (n = 30, a proposed threshold for successful implantation) had longer COC usage compared to the rest of the women. Authors this could be mediated by the effects of OCs on stem cells in an inactive endometrium. In particular, some authors have said this effect after long-term use of OCs is "infrequent but persistent" [28]. These results should be taken cautiously and require further confirmation in larger groups of healthy women in prospective studies; as we will discuss later infertility has not been associated to OC.

The effects of COCs on gonadotropins have also been studied: Compared to women who never used COCs, women using them showed similar or slightly lower FSH levels, whereas women who used them showed slightly higher FSH levels that seemed to wane over time. (LH showed a similar pattern, but it was only significant in one of the two study groups). The authors attributed this to a possible rebound effect of gonadotropins after withdrawing the hormonal COC and a suppression of endogenous estrogen and progesterone [29]. After withdrawal of COCs normal physiology is gradually restored: in a study with 24 women it was observed that the first cycle is longer and with lower gonadotrophin levels compared to the third cycle; ovulation changes were observed in 17/24 women in the first cycle and in 21/24 women in the third cycle [30]. Recent use of OCs and their long-term use have been associated with longer follicular phases (longer time to ovulation) by some authors, but they acknowledged there are conflicting results on this issue in the literature and many women might choose to start using OCs to help regulate their cycles, which might already be longer [31].

Estrogens are known to stimulate prolactin production. Some reports associated post-pill amenorrhea and galactorrhea and serum prolactin is elevated in OC users; this is more pronounced in women who use high-dose OCs but not significant association was found with long-term usage [32]. However prolactin levels do not seem to be altered in women who previously used COCs [33].

2.3. Return to fertility

Despite these described biochemical or histological findings, the reversibility of OCs has been clinically observed for decades and across many different ethnic groups (**Table 1**); many studies have reported 1 year pregnancy rates between 70 and 90% and 2 years pregnancy rates of 80–90% [1, 34].

In the 1960s, the "postpill amenorrhea syndrome" was described as amenorrhea, anovulation and reduced reproductive fecundity for more than 1 year following discontinuation of OCs in some women who previously had regular menstruation. Some authors noted that many women with this syndrome exhibited oligomenorrhea before starting oral contraceptive usage [35]. It was thought that the exogenous administration of hormonal therapy with OCs delayed the return to normal function of the hypothalamic-pituitary-ovary axis [36]. Some authors advocated "watchful waiting" in women not seeking pregnancy, mentioning that regular menses tend to reappear after 12–18 months, and emphasized the importance of ruling

	Study design	Method	Participants	Subjects	Exposure (months)	1-year pregnancy rate	2-year pregnancy rate	Comments
Pardthaisong [34]	Retrospective and Prospective: 2 arms	Depo provera (DMPA) vs. IUD	796 DMPA vs. 125 IUD	Mean age:24.5 vs. 27.7	Not reported	78.2 vs. 79%	92.1 vs. 93.3%	Median delay to conception: DMPA: 5.5 months. IUD 4.5 months
Harlap and Baras [109]	Retrospective		1403 OC 4477 other contraceptives			The proportion of pill users who conceived in the first month was 30% less than the others, but by the third month this difference had disappeared		
Belhadj et al. [110]	Randomized, prospective	Mirena IUD 20mcg/d vs. CuT380Ag	110 females			>90%		Median time to planned pregnancy was 3 months for the TCu 380 Ag group and 4 months for the Levonorgestrel 20 group
Skjeldestad et al. [111]	Prospective observational	Copper IUDs	101 IUDs users (Nova T, MLCu 250 vs. MLCu 375) Norway	Mean age 28.3	56% <24m	85%	93%	
Affandi et al. [112]	Prospective	Implant	80 Implanon vs. 80 Norplant Indonesian women	Mean age ~28.0 y. Mean parity ~ 2.3	35.3 ± 13.1 vs. 55,8 ± 17.7	48.8 vs. 37.5%	60.0 vs. 73.8%	
Wilson et al. [106]	Prospective	IUD	1051 IUD. New Zealand	375 nulligravid 676 gravid women	Not reported	Not reported	91.5 vs. 95.7%	Removal because of complications: No reduction in fertility or increase in ectopic gestation, miscarriage, or preterm delivery rates in 12 months
Gupta et al. [113]	Prospective	IUD (8 types: 6 Cu-bearing, progestasert IPCS 52 and Lippes Loop)	91 users India.	Mean age ~27.6	22.9 m	92.3%	96.7%	
Silvin et al. [114]	Prospective, multicenter	Norplant vs. Norplant II	178 users (62 vs. 116)	Mean age ~ 27.45	Mean 31, 35 months	83 vs. 84%	87 vs. 92%	

	Study design	Method	Participants	Subjects	Exposure (months)	1-year pregnancy rate	2-year pregnancy rate	Comments
Randic et al. [115]	Prospective,		748 parous (planned pregnancy) 2713 (complications)	Mean age: 27.1 (first group)		82.9%	89.5%	
Andersson et al. [116]	Prospective	IUD	209 IUD users (71 Nova-T vs. 138 IUD – LNG)	Mean 27 y	Median 21 months (range 6–53)	71.2 vs. 79.1%	79.7 vs. 86.6%	
Tadesse [117]	Prospective	Copper T200	780 users. Ethiopia	Mean age 29 Nulligravid: 3.2% multip. 93.5% grand multip: 3.3 %	Mean 3.5 years	86.6%	No data	
Buckshee et al. [118]	Prospective	Subdermal Implant (Norplant II)	627 India	18–35 years	Mean 55.8 ± 17.7 m	80.3%	88.3%	
Bahamondes et al. [95]	Prospective	Injectable (Cyclofem)	70 users Brazil, Chile, Colombia and Peru	Mean age ~25.6	Mean number of injections: 7.1 ± 4.6	82.9%	Not reported	Return of fertility was not related to the woman's age at the time of discontinuation, her weight, or the number of Cyclofem injections.
Zimmerman et al. [119]	Prospective observational	OC	348 users of 30 mcg EE / 2 mg DNG (Valette)	Mean age: 26.8 y	Median 4–6 months	95%	Not reported	
Delbarge et al. [120]	Prospective	IUD Gynefix	128 users	Mean age 30.5 y	104.6 ± 93.5 weeks	88%	99%	No statistical differences in pregnancy rates were found for age and duration of use of the IUD
Farrow et al. [42]	Retrospective	OC	8497 users who conceived intentionally South-west England	Mean age 28	From 1 to more of 5 years: >5: 56.8% of the participant 3–4: 20.3%, 1–2: 11%, <1: 7%, never: 4.9%	According to years of use: >5: 89.5%, 3–4: 88%, 1–2: 85.2%, <1: 83.5%	Mean 96.6%	The article includes many analysis categories, such as woman's alcohol consumption or cigarettes smoked

	Study design	Method	Participants	Subjects	Exposure (months)	1-year pregnancy rate	2-year pregnancy rate	Comments
Hov et al. [121]	2 branches. A: Prospective	Copper IUD	205 users Norway (A: 109 IUD removed due to wish to be pregnant vs. B: 96 IUD removed due to complication)			90% (group A).	93.6 vs. 98%	No difference in cumulative probability to become pregnant by parity, duration of IUD use and age upon removal of IUD
Wiegratz et al. [44]	Prospective observational	OC: 30 microg ethinyl E2 and 2 mg dienogest (Valette)	706 users Germany	Mean age: 26.8	21.5m ± 16.8m (median 16m)	86.6% (more than 15.5% in the first 3 cycles) Meantime 3.5 cycles	not reported	
Cronin et al. [46]	Prospective cohort	OC (drospirenone and other progestins)	2064 users	Mean age 28.1 years	2.8 ± 0.8 years	21.1 % after first circle. 79.4% 1-year	88.3%	
Stoddard et al. [122]	Prospective	IUD	69 IUD (50 Cu, 19 LNG) vs. 42 non IUD. St Louis, USA.	Mean age: 27.6 vs. 29.5		81 vs. 70% (p=0.18)		
Abdinasab et al. [123]	Retrospective cohort study	Cu IUD (T-380)	750 non-nulliparous Iranian women 375 Cases: history of using Cu T-380A IUD > 5 months. 375 Controls: history of other contraceptives: OCP, withdrawal method, male condom.	Mean age: 34.8 vs. 33.9	57.46 ± 47.74 m			Mean length from Cu T-380A IUD removal to pregnancy was 14.87 ± 5.18 months

Table 1. Studies evaluating return to fertility.

out other causes of amenorrhea [37]. Some women with amenorrhea after discontinuing OCs could have preexistent menstrual irregularities masked by OC. In the 1980s more reliable studies showed no association between oral contraceptive use and secondary amenorrhea and lack of specific findings in this syndrome [38]. Current practice holds that women who do not menstruate 3 months after discontinuing COC usage should be evaluated like any woman with amenorrhea [39].

Diana Mansour published in 2010 an interesting comprehensive review of the literature assessing pregnancy rates following discontinuation of several contraceptive methods; 17 prospective studies were included. One year pregnancy rate following cessation of OCs (3 studies) ranged from 79.4 to 95% and median time to pregnancy, estimated from available data, was 2.5–3 cycles) [1].

The Oxford-FPA study, published in 1978, was one of the first studies that investigated this issue. In this prospective cohort study 12 months after contraception cessation 70.1 of women who used OCs remained undelivered, which is significantly higher than 46.4% for the diaphragm group or 47.6% for the other methods group. After 36 months the differences became non-significant [40].

Doll et al [41] performed a study in nulliparous women from 17 family planning clinics in England and Scotland; they found that duration of oral contraceptive use was linearly associated with decreased fertility and that return to fertility is slower in users ceasing OC (32% delivery after 1 year) compared versus users ceasing IUD (39%) or users abandoning barrier methods (54%); 18 months after ceasing using contraceptives these values were 70% delivery for previous OCs group, 67% delivery for previous IUD group and 76% delivery for the barrier method group. Authors observed significantly faster return to fertility for users of barrier methods (log rank test, $p = 0.002$) without statistical differences between OCs and IUDs. Other studies usually report around 1-year conception rates (>80%) [42]. Temporary (a few months) delays in fertility have been observed in other studies in women using OCs [43, 44] and reflect physiological changes: some women return to fertility faster than others. In this study duration of OC use had no significant effect on fertility and women who interrupted OCs and used barrier methods for 3 months had faster return to fertility than those who tried to conceive immediately after stopping using OCs [41]. After 42 months of ceasing OCs 11% of women had not delivered a baby.

A recent Danish prospective cohort study also observed a temporary reduced fertility in the 3 months after OCs discontinuation compared to barrier methods, but pregnancy probabilities became similar thereafter [45]. From the Kaplan–Meier curves time to pregnancy (TTP) percentiles were obtained, the 25th, 50th (median) and 75th percentiles were 2, 3 and 7 cycles for women who had discontinued barrier methods and 2, 4 and 9 cycles for women whose last method were OCs. A dose–response relationship between time using OCs and increased fecundability was observed, with confidence intervals becoming significant after 10 years of use. High-dose OCs was associated with shorter TTP. This study has some limitations, but the conclusion is very reasonable: there is no evidence that using OCs for years impairs fecundability. Other studies have also showed that long-term OC use is not associated with reduced fertility [46], but not all studies agree on this matter [47].

The effect of other variables (weight, smoking …) on time to fertility after OC discontinuation has been evaluated in many studies, but small sample sizes limit the interpretation of these results [1].

Many studies do not evaluate COCs and POP separately or focus only on the former. POPs have not exhibited delays in the return of fertility [48]. With Norgestrel pills conception can occur within once cycle of stopping the medication [49]. In a randomized open-label study with 103 women after discontinuing a desogestrel-only pill ovulation appeared as early as 7 days, with an average of 17.2 days; [50] (with traditional POP ovulation occurs in 30–40% of users, but this pill has a remarkable anovulatory effect shared with combined formulations).

Emergency oral contraception (mifepristone) does not harm future fertility [51] and woman should be informed that emergency oral contraceptives do not protect from future pregnancies. In women who had successful abortive expulsion of the gestational sac the mean times to ovulation after mifepristone administration was 20.6 days (±5.1; range 8–36) [52].

2.4. Pregnancy complications and outcomes

Some studies have linked previous OCs usage with **twin conception** [53, 54, 55], whereas others have not observed this association or limited its findings to OCs with high doses of estrogen [56]. Increased levels of FSH are observed in mothers of twin pregnancies; the "endocrine hypothesis" of dizygotic twin pregnancies holds that high FSH is responsible for multiple ovulation [57]; it has been suggested this mechanism might be the link between OC usage and dizygotic twin conceptions. However many of the studies reported increased monozygotic twins rates. More recent evidence is lacking on this matter.

The effect of OCs on **fetal loss** has been studied for many decades. The first studies did not find any link or described the effect of OCs as protective [53]. Some studies have shown consumption of oral contraceptives for more than 9 years could protect against miscarriage [58]. On the other hand a Spanish retrospective [59] case–control study (N = 300) did actually identify taking oral contraceptives for more than 2 years before pregnancy as a risk factor of miscarriage (OR: 2.56, 95% CI: 1.16–5.67); the statistical methods included a step-wise regression, a controverted statistical procedure known for its risk of spurious associations. The authors hypothesized that the endometrial atrophy associated to taking (modern) low-dose oral contraceptives for extended periods of time could cause miscarriage or that acquired activated protein C resistance could be the link between oral contraceptives use and miscarriage.

A Danish prospective cohort study published in 2016 did not confirm these findings; 4500 women participated in this study. The hazard ratios were all non-significant and smaller than 1; the study did not find association between spontaneous abortion and discontinuing oral anticonceptives closer to conception (categories: discontinuing 0–1 months before conception, 2–6 months or 7–12 vs. discontinuing more than a year (reference) before conception); or between spontaneous abortion and longer use of oral contraceptives (comparing less than 4 years COC usage (reference) vs. 4–7 years, 8–11 years and equal or more than 12 years) [60].

The Jerusalem Perinatal Study is a cohort study that recorded several variables on 92,408 live neonates and stillbirths from the 1964–1976 period and on their families; these data were linked to several registries and many epidemiological studies were carried out [14]. For instance, in this study former COC usage conferred no risk of obstetric complications [61].

The relationship between OCs and **birth weight** has been controversial in the literature. A study with 260 Boston women found previous OC use increased birthweight and placental weight compared to non-users [62] with more pronounced effects in women with longer use and with stronger hormonal contraceptives. The authors suggested this effect might be mediated by the higher levels of estradiol and progesterone observed in former users.

A 2015 Danish prospective cohort study evaluated the effect of oral contraceptives usage before pregnancy on birth weight [63]. The authors used data from online questionnaires and from the Danish Medical Birth Registry; 5921 women were followed for 12 months and 4046 live births took place. After adjustment for several confounding variables women who had discontinued OCs less than a month before conception exhibited higher mean birth weight (97 g, 95% CI: 26–80 g) compared to those who discontinued more than 12 months before conception; and lower mean birth weight was observed in women with previous >12 years of OCs use vs. <4 years (−85 g, 95% CI: −158, −11).

Previous use of OCs has not been consistently associated with **birth defects** on the offspring. Some studies old studies found this link [55] but other studies did not. In a cohort (n = 732) from the Jerusalem Perinatal Study children were tested up to 3 years age. Although some dim trend in IQ values was suggested, those whose mothers were OCs users did not exhibit statistically significant differences in weight, height, development quotient or intellectual quotient [64].

It might occur that a woman accidentally and unknowingly takes oral contraceptives for some period after conception, a situation sometimes called **breakthrough pregnancy**, thereby exposing the fetus to doses of estrogens or progestins. This situation is especially worrying and distressing for affected women. In the past a frequent case of fetal exposure to potent oestrogens was that of women prescribed diethylstilbestrol (DES) in pregnancy to prevent abortions; after a study [65] linked this to vaginal clear-cell carcinoma in 1971 the FDA banned this drug in pregnant women. The daughters of women treated with DES in pregnancy have shown increased risk of cervical and vaginal precancerous states, a possible slight increase in breast cancer in women older than 40 years old, reproductive tract structural anomalies, infertility and pregnancy complications. The sons of treated women may be at increased risk for epididymal cysts and maybe other genital abnormalities. The NIH and the CDC provide information for healthcare providers and patients on this public healthcare issue [66, 67].

Several studies have evaluated how the use of oral contraceptives with way less estrogenic potency compared to DES after conception could influence male hypospadias and urinary tract anomalies, but the results have been inconclusive and contradictory: In some studies the association was clear [68], but others did not observe this association [69]. A recent 2009 large Danish case–control study evaluated the relationship between use oral contraceptives after conception and male hypospadias. This study used prescription data rather than self-reported maternal exposure data in order to prevent the recall bias, a relevant cause of spurious associations in retrospective case–control studies. The adjusted prevalence ratios were close to one and none of them was significant: for example 0.85 (95% CI: 0.65–1.28) for exposure to COC in early pregnancy and hypospadias detected within 6 months postpartum [70].

Women with **breakthrough pregnancies** or conception close to OCs cessation should also be assured large studies have not identified increased prevalence of **birth defects**. A meta-analysis published in 1990 found no association for OC exposure early in pregnancy and heart defects or

limb reduction defects [71]. Charlton et al. collected data on OCs use and major birth defects on 880,694 live births from Danish registries; the prevalence of major birth defects (per 1000 births) was 25.1 for never users of OCs, 25.0 for OCs used more than 3 months before conception, 24.9 for OCs used less than 3 months before conception and 24.8 for OCs used after conception; the confidence intervals were not significant, and association was not found either for prevalences by defect subgroup [72]. Older studies (with older contraceptive formulations) arrived to more or less similar results: No significant association was observed between congenital malformations and conceiving within 1 month of stopping OC, and in breakthrough pregnancies the ratio of observed to expected major malformations was only significant in mothers one pack or more of cigarettes daily [73]. A recent study in 2010 (with 4000 healthy controls and 9986 infants with birth defects) did not find association for 32 anomalies when OCs usage took place before conception and only found association for gastroschisis (OR 1.82, 95% CI 1.25–1.67) and hypoplastic left heart syndrome (OR 2.33, 1.28–4.25) when OCs usage took place afterwards [74].

POPs have some particular characteristics regarding pregnancy outcomes. If the contraception fails a higher incidence of ectopic pregnancy versus other contraceptive methods has been described, but the incidences were similar to those in women not using contraceptives [12]. A proposed explanation is a reduction in the activity of fallopian tube cilia and tubal motility alteration [75]. Fetal male hypospadias was more likely to occur among women who took progestogens to prevent pregnancy complications or to help with becoming pregnant between a month before conception and 3 months after this point (reaching adjusted OR > 3, and stratified OR > 2). However the association was non-significant for those women who took progestogen as a contraceptive [76].

A Norwegian study published in 2015 evaluated the risk of preterm birth and found this risk varied depending on the moment of exposure and the progestin used. COCs with Norethisterone were particularly associated with preterm birth in some exposure periods (with adjusted OR reaching 3.33 (95% CI: 1.69–6.57 for the period 0–12 weeks after conception, a period that seemed particularly critical in some subgroups); for COCs with Drospirenone or Levonogestrel or POPs the association seemed weaker or absent. Authors noted the association for preterm birth seemed consistent across all exposure periods, but they also acknowledged other confounding factors could explain this association. Authors pondered a weakly estrogenic environment could be deleterious for fetal growth. The study also evaluated birth weight using z-scores (a more precise and current definition) and found no association with OCs [77]. A cohort study in China agrees with this association (OR for OCs usage in multiple logistic regression: 8.162, 95% CI: 1.622–41.072) [78]. Other studies found that exposure to OCs in the 6 months before conception was associated with higher birth weight compared to longer duration exposures [63].

There is no evidence that Emergency Contraception is associated with worse outcomes in future pregnancies. The pregnancy outcomes of women undergoing mifepristone-induced abortion were studied in nearly 15,000 pregnant women in China. There were no statistically significant differences in preterm delivery, frequency of low birth weight or mean infant birth weight when comparing these women with those with surgically induced abortion. When comparing mifepristone-induced abortion and women without previous abortion the former had higher mean birth weight and no significant differences in pregnancy length [79]. Other studies have found the outcome of medically terminated pregnancies is similar to those of mothers without them and better than those of mothers with surgically terminated pregnancies [80].

Some authors have noted in the last years we have observed increasing rates of OCs use as well as increasing rates of Autism Spectrum Disorder diagnoses and have raised hypotheses regarding specific consequences in the offspring; this remains to be elucidated in future clinical studies [81].

2.5. Conclusion

It seems clear that fertility returns promptly with OCs and that any delay to return to normal physiology does not remarkably influence 1 year or longer fertility rates. There's no consistent evidence to conclude OCs are associated with future miscarriage, preterm birth, low birth weight or hypospadias.

3. Implants and rings

Removing the implant is often an easy and uncomplicated procedure. In a clinical trial performed by Bahamondes et al., women perceived the pain of the as none (444, 86%), mild (65, 13%), moderate (8, 2%) or severe (0) for the ENG (etonorgestrel) implant; and none (252, 81%), mild (49, 16%), moderate (6, 2%) or severe (1%) for the LNG (levonorgestrel) implant [82]. The ease of removal was reported as easy (492, 94%), slightly difficult (22, 4%) or difficult (8, 2%) for the ENG implant and easy (254, 81%), slightly difficult (47, 15%) or difficult (12, 4%). In this study, two (0.4%) ENG removals were complicated (the implant broke) and seven (2.2%) LNG removals were complicated (in seven cases the implant broke).

The ACOG has published some recommendations regarding the clinical challenges posed by LARC, including the implants [83]. Ultrasonography can be helpful if the implant is impalpable when removal is attempted [84]; in rare cases magnetic resonance might be required to locate it.

There is no evidence fertility is delayed after removal of contraceptive implants [13]. In a study Etonogestrel became not detectable within 1 week of removal of Implanon® implant [85]. Pregnancies have been observed to occur as early as 7–14 days after removal [86]. Within 1 month of Implanon removal ovulation has been observed to return in 40% (16/40) women; and 12 months conception rate was 96% (23/24) in women who had the implant removed and did not implement other contraceptive methods [87].

NuvaRing® is the only ring available to the United States; it releases 15 μg ethinyl estradiol +120 μg etonogestrel per day (which are rapidly absorbed through the vaginal epithelium [88]) and lasts 3 weeks. Ovulation returns after removal of the vaginal ring (in a mean time of 19 days [89]). In the majority of women who discontinue NovaRing ovulation and spontaneous menstrual cycles return within a month [90].

Many other contraceptive preparations are being developed, and prompt return of fertility is usually the rule. After discontinuation of a transdermal patch ovulation has been described to return in the first cycle in 86% of women [91].

The considerations on pregnancy outcomes for OCs can be extrapolated to those methods in which estrogens and progestogens are administered non-orally.

4. Injectable contraceptives

Injection-based methods differ from other methods in the return to fertility since they are irreversible in the short-term, but fertility rates eventually reach those of them [13]. In this group methods one year pregnancy rates range between 72.5–82.9% with median time to pregnancy being 4.5–5 months [1].

Depot medroxyprogesterone acetate (DMPA) is the most commonly used injectable, being administered as intramuscular injections every 12 weeks. Product leaflet mentions some pregnancies have occurred 14 weeks after a preceding injection but longer delays are common: the observed mean time to ovulation is 5.3 months and the median time to conception is 10 months after the last injection. About 83% women should conceive within 15 months of the last injection [92].

A large study in over 1000 Thai women remarked that return to fertility and proportions of live births in the offspring of women who used MDPA are similar to those of women using other contraceptive methods (OCs or IUDs): in this study the median delay to conception for MDPA was 5.5 months plus the estimated effect duration of the last injection; this can be compared to 3 months for OCs and 4.5 months for IUD [93].

Intramuscular injections of norethisterone enanthate acts as a contraceptive for 8 weeks; in 11 of 20 women discontinuing this method follicular activity was observed within 90 days of the last injection [94]. The observed median delay to conception is 6 months after the last injection; 14 of 40 women became pregnant within 12 weeks and 31 of 40 after 1 year. Authors remarked the real figures could be higher. The delays in fertility were not correlated with the duration of use.

Intramuscular injections of estradiol cypionate and medroxyprogesterone acetate (Cyclofem®) are administered every month. 1.4% women became pregnant at the end of the first month (since the first missed injection), 52.9% after 6 months and 82.9% after 9 months. Pregnancy outcomes were favorable: 51 (94.4%) pregnancies ended in a live birth [95].

5. IUD

5.1. Use cessation

The procedure to extract the IUD is often uncomplicated. A speculum and a Foerster clamp are needed: The speculum is inserted into the vagina until the cervix and the IUD threads appear through the external cervical os. The threads are fastened with the clamp and pulled until the total extraction of the IUD. The best time for extraction is during menstruation since the cervical os is slightly more dilated than under normal conditions. Non-visualized IUD strings is a potential challenge, the most common cause being string retraction into the uterus. ACOG recommends sweeping the cervical canal with a cytobrush, a maneuver that often reveals them; if this is not effective, the algorithm includes ruling out pregnancy, confirming abdominal location of the IUD and evaluating the need for a laparoscopic removal [83]. Some women might describe slight temporary mood swings after LNG IUD removal.

5.2. Physiology

IUDs elicit foreign body reactions, which turns the intrauterine milieu lethal for embryos, without significant extrauterine effects. In addition to this, different types of IUDs can alter previous processes through varying degrees: Mucus thickening, glandular atrophy and stromal decidualization in LNG IUDs, spermatozoa decay and toxicity by Copper ions in the uterine cavity, transmission of noxa from the uterine lumen to fallopian tube, etc. [96, 97]. The histological changes were found to be reversible within some months. Unlike OCs, IUDs have not been observed to be associated with follicular phase length [31].

5.3. Return to fertility

Fertility is not impaired after IUD removal13. In Diana Mansour's bibliographic review 1 year pregnancy rates for Copper IUDs were 71.2–91.1% for Copper IUDs and 79.1–96.4% for LNG IUDs (median time to pregnancy were 2–3.7 cycles and 4 cycles respectively)1. Currently there is no evidence of a delay in return to fertility after using an IUD [13]; in some studies >50% of women conceived within 3 months after discontinuing it [98]. **Table 1** contains selected studies pertaining return to fertility after contraception.

The history of IUD devices includes some particular case of long-lasting health and reproductive consequences after IUD usage. Despite some previous attempts and projects some decades earlier, it was not until the 1960s that commercial IUDs made their way into the market with the approval of the Lippes Loop and the Safe-t-coil by the FDA in 1966. The **Dalkon shield**, introduced in 1971, attempted to increase the surface of the endometrium in contact with the IUD and to increase retention rate; it included a multifilament tail string encased in Nylon [99]. Several reports associated this IUD with increased infection rates, septic abortions and deaths; apparently the multifilament string could allow vaginal bacteria to access the uterus. Since this IUD was used in many world countries the numbers of women suffering adverse consequences is difficult to estimate. Device sales stopped in 1974 and the company started to recommend device removal if a pregnancy took place, which is now standard practice; women experiencing the adverse events, which includes fertility impairment as sequel, filled many lawsuits and in 1980 the company recommended removal of the Dalkon shield in women who were still wearing them. Distrust and doubt regarding IUDs lasted for several years after this, especially in the USA [100].

The relationship between IUD usage and pelvic inflammatory disease (PID), a well-known cause of infertility, has been studied extensively for decades [101] and many studies had pitfalls [102]: Sexual habits as a confounding factor, diagnosis bias… The described incidence of pelvic inflammatory disease on IUD users is very low (1.6/1000 person-years) and particularly confined to the first weeks after insertion. Preventive strategies include adequate selection of IUD candidates, prophylactic antibiotic during insertion, careful monitoring and treatment of infections, etc.

Long-term usage is not associated with posterior infertility; several studies have shown pregnancy rates are not delayed in women who used copper IUDs for several years [106]. Zhu et al. performed a study with 1770 Chinese women who had their IUDs removed after a catastrophic earthquake in the Sichuan region and were followed up for two years [103]. 71% women conceived within 1 year after removal and 80% conceived within 2 years. In the multivariate logistic regression analysis age was negatively associated with fertility (OR 0.7548, 95% CI: 0.7148–0.7933), while duration of IUD use (OR 1.0596, CI: 1.0244–1.0960) and previous

gravidity were positively associated. The authors described a clear reduction in fertility and increased miscarriage rates with age; 1 year pregnancy rate among women older than 40 years was 49.67%. They reported duration of IUD use was associated with decreased fertility but did not stratify the analysis of this variable and age could be a confounding factor. Women with longer IUD usage are also older women, and fertility and miscarriage rates are known to depend on age.

In the study by Doll et al [41] long-term IUD usage was associated with reduced fertility (log rank test for linear trend, P = 0.0035); authors hypothesized that this might be related to pelvic inflammatory disease This article received media coverage in the UK [104, 105], but remarking that most IUDs in this study were not available for women anymore and that current standard practice included better diagnosis of infections. The posterior NICE Guidelines evidence review highlights that IUD female users were older and had higher rates of miscarriage, termination and ectopic pregnancy [13] and concludes that there is no evidence on delay in the return of fertility after discontinuing IUD usage. This also applies to nulliparous women, whose uterine cavity is usually smaller [15].

5.4. Pregnancy outcomes

One common concern of IUD users is the outcome of their future pregnancies. The different pregnancy outcomes observed in many studies with Copper IUD range from 84 to 88% for live births, 88–82% for term deliveries, 6–12% for spontaneous abortions, 1–4% for induced abortions and 0–2% for ectopic pregnancies (the studies classifications were not uniform) [1]. For LNG IUD the pregnancy outcomes are similar. Pregnancy outcomes of several studies are reported in **Table 2**.

Many studies have assessed the effects of IUD complications on fertility. In a 1989 study with copper IUDs by Wilson et al. with Neo-Zealand woman 16% (164) of IUD removals took place due to complications. 92.4% of these women had conceived after 36 months (compared with 94.2% for the rest of IUD removals). Regarding pregnancy complications slight significant differences were observed only between some subgroups, which could be related to multiple comparisons in this study; for example in women who used IUD for less than 24 months, nulligravid women had smaller conception rates than gravid women (86.7 vs. 93.6%, $p < 0.005$) [106]. Authors noted the observed outcomes in IUD users were similar or better compared to population ones. Other studies have also noted IUD removal was not associated to ectopic pregnancy risks [115].

In the unlikely event that a woman using IUD becomes pregnant it is advised that the device is removed before 12 completed weeks' gestation, regardless of whether she wants or not to continue with the pregnancy [13]. These situations are associated with significant miscarriage and septic abortion risks.

Regarding PID, a dose–response has been established between the severity and number of episodes and ectopic pregnancy risk; for example in women aged 25–44 with 2 or more severe episodes the probability has been statistically modeled to be 84% [107]. These women have many options: careful follow-up, laparoscopy, in vitro fertilization, etc.

	Method	Participants	Term pregnancy (%)	Miscarriage (%)	Ectopic (%)	Preterm birth (%)	Induced abortion	Comment
Belhadji et al. [110]	TCu380Ag	17 pregnant women	88%	12%				
Wilson et al. [106]	Copper IUDs	1051 IUD. New Zealand	83.2%	11.6%	0.5%	2.0%	2.7%	Similar rates to women from New Zealand, but higher rates of induced abortion. Authors attributed this to women's attitudes and choices after the recall of another IUD.
Skjeldestad and Bratt [111]	Copper IUDs	95 pregnant women	88.4%	8.4%	2.1%		1.1%	
Andersson et al. [116]	IUD	50 users	84%	6%	2%		4%	2% outcome unknown and 2% still birth
Sivin et al. [114]	IUD TCu380Ag	66 pregnant women	82%	15%	0%		3%	
Tadesse, [124]	IUD Copper T-200	671 pregnant women	87.8%	8.5%		3.7%		
Randić et al. [115]	IUD.	3461 Croatian women	Ectopic pregnancy: Control: 3.9%, planned pregnancy (parous women) 2.7%: accidental pregnancy 0%; expulsion/displacement 1.2%; bleeding/pain + PID 6%. (Non-significant differences)					Lower rates than general population
Andersson et al. [116]	LNG-20 IUS	104 pregnant women	85.6%	5.8%	1%		2.9%	
Sivin et al. [114]	LNG-20 IUS	68 pregnant women	89%			2%		
Belhadji et al. [110]	LNG-20 IUS	22 pregnant women	86%	14%				17 women still pregnant at time of analysis
Buckshee et al. [118]	Norplant II	136 pregnant women	89.7%	4.4%			5.9%	
Sivin et al. [114]	Norplant II	86 pregnant women	88% (term delivery)	8%	1%	1%	2%	
Sivin et al. [114]	Norplant	33 pregnant women	93% (term delivery)	4%	0%		4%	
Diaz et al. [125]	Norplant	75 pregnant women	79% (term delivery)	9%		5%		

	Method	Participants	Term pregnancy (%)	Miscarriage (%)	Ectopic (%)	Preterm birth (%)	Induced abortion	Comment
Bahamondes et al. [95]	Cyclofem-monthly	58 pregnant women	98.4%	3.4%				
Hahn et al. [60]	OC	4862 Danish	85.7%	14.3% (SAB)				No evidence that pregravid OC use is associated with spontaneous abortions
Chen et al. [79]	Medical abortion (mifepristone) vs. surgical abortion vs. no abortion	13928, Chinese				2.9 vs. 3.0 vs. 3.7 (P<0.05)		Authors concluded no long-term consequences

Table 2. Pregnancy outcomes after using contraceptives.

6. Other methods

Return to fertility with barrier methods is prompt and expectable, given the lack of effects on female physiology compared to other methods. The figures have been reported previously as reference group. One year delivery rate after discontinuation was found to be 54% in an English study, which was higher than COCs or IUDs [41].

Natural family planning does not involve persistent physiological changes on women; 1 year pregnancy rates and spontaneous abortion risks can be considered as similar to general population ones. For example, a study observed abortion rates of 10.1% [108].

7. Clinical cases pertaining return to fertility

Case 1: barrier method of contraception.

An 18-year-old woman comes to a consultation for contraceptive advice. She has just started a relationship.

Personal history: without interest.

Family history: DM type II father. Mother HTA.

Menarche at 14 years.

Not pregnancies.

Planning: has not started relationships.

The most appropriate method? In this case the most appropriate method would be barrier contraceptives, since she does not yet have a stable relationship. If the patient requested it combined oral contraception could be considered, but in that case we will recommend to keep using barrier methods to prevent STDs (double contraception).

Case 2: Combined contraceptives (oral contraception).

Female, 26 years old. Stable couple for 2 years. She wants advice on contraception. She remarks she wants to have children at some later point in her life.

Personal and family history: no interest.

Menarche at age 13.

Nulliparous. Last cytology less than 1 year ago.

Menstruation: 6/30, quite irregular. Dysmenorrhea.

Previous recommendation: Barrier method (condom).

The most appropriate method? In this case we can recommend her oral combined contraceptives, since she has no remarkable diseases, has a stable partner and this will help in her dysmenorrhea and menstrual pattern. We can assure her the reversibility of oral contraceptives has been observed for decades and that after interrupting them women's fertility will be similar to the rest of women. She opts for oral contraception.

Case 3: Combined hormonal contraceptives (vaginal ring).

30 years old Woman with stable couple for 8 years. Uses oral combined contraceptives. She wants to stop taking a pill every day. She wants to have children at some point in the future and is afraid of pregnancy complications.

Personal and family history: no interest.

Not pregnancies. Last cytology 2 years ago, results: normal.

Menarche: 15 years.

Menstruation: 4/28, from taking contraceptives.

Planning: Combined oral contraceptives.

The most appropriate method? After explaining her the alternatives, she decides that she prefers the vaginal ring. We recommend how to start using this method after taking oral contraception. The ring should be administered as later the next day after the termination with the current pill. If the pill pack also has inactive tablets, she should start using the ring the day after the last inactive tablet.

Case 4: Subdermal Implant.

33 years old woman, she gave birth to a healthy son 2 years ago. She carries a subdermal implant and wants to become pregnant again.

Personal history: without interest.

Family history: Mother with breast cancer.

Pregnant: 3 years ago.

Menarche: at 15 years.

Menstruation: 4/28.

Plan: Remove the implant, preconceptional counseling.

The implant is palpable and removed successfully. We advise her to wait for her period before attempting to conceive.

Case 5: IUD.

Female 34 years old. She does not want more children at the moment, but she does not want irreversible contraception since she does not know if she will want children in the future. She does not want to take oral contraception.

Personal and family history without interest.

Menarche to the 14 years.

Two vaginal births, 2 and 4 years ago.

Menstruation: 4/27, are not very abundant.

Planning: use a condom.

The most appropriate method? In this case we could offer the administration of an IUD, since it is reversible, but can last up to 5 years. We explain her that there is no conclusive evidence that long-term use of IUD leads to impaired fertility. Many other factors influence fertility, like aging or smoking.

Case 6: Irreversible.

A 42-year-old woman who visits her doctor after a 7-day menstrual delay. Demand planning advice.

Personal history: Hypothyroidism under treatment, varicose syndrome, smoking 15 cig / day. Intolerant to metallic chromium.

Menarche at age 12.

Two pregnancies and vaginal births, babies of 3900gr and 4100gr at 31 and 38 years.

Menstruation: 7/26, abundant since always.

Planning: coitus interruptus, because her husband does not "tolerate" the condom. Gynecological review less than 1 year ago with ultrasound and cytology, without alterations.

Conduct to follow: pregnancy test is performed, being negative. Menstruation at 3 days.

Which contraceptive method is the most appropriate? Given her age, having two children, the personal history, for this couple the best method of contraception would be vasectomy or tubal ligation.

8. Conclusions

None of the contraceptive methods described (OCCs, POP, emergency contraception, implants, rings, Cu IUD or LNG IUD) is associated with impaired fertility. A temporary delay in fertility can occur with COCs, but this does not alter 1 year conception rates significantly. Injectable contraceptives are associated with delays in fertility buy not with fertility impairments.

Previous OCs usage is not associated with birth defects and their effect on birth weight or preterm birth seems small and controversial (some associations have been detected in recent large and powerful studies, but a causal link remains to be confirmed).

In adequate large studies previous IUDs (Cu or LNG) usage has not been consistently associated with adverse pregnancy outcomes. There is not enough evidence to support the hypothesis that long-term IUD harms future fertility.

Preconceptional counseling is advisable for all women who want to abandon contraception to get pregnant.

Author details

Blanca Patricia Bautista Balbás[1]*, Luis Alfredo Bautista Balbás[2] and Alicia Pouso Rivera[3]

*Address all correspondence to: blancabautista91@gmail.com

1 Midwife at Hospital Can Misses, Ibiza, Spain

2 Clinical Analysis Laboratory, Hospital la Paz, Madrid, Spain

3 Midwife at Hospital Belen, Madrid, Spain

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