Hormonal Contraceptives and Post-fertilization Effects

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ABSTRACT: Hormonal contraceptives are widely used for birth control and therapeutic purposes. The mechanism of action proposed for these compounds can be found in several scientific journals published to date. The present work consists in a scoping review of a convenience sample of papers regarding the mechanisms of action of each of the three main classes of hormonal contraceptives available. Different parameters and biological consequences associated with their use were also reviewed. Based on these data, we evaluated the probability of embryo loss due to the use of hormonal contraceptives. Evidence indicates the probability of embryo loss due to post-fertilization effects.

***Keywords*: Abortifacient, Embryo loss, Hormonal contraceptives, Ovulation inhibition, Post-fertilization effect.**

Introduction

In 1951 Carl Djerassi synthesized the first oral active progestin, norethindrone (SHOUPE; KJOS, 2006, p. 15). Subsequent discoveries led to the addition of mestranol, a synthetic estrogen, to the norethindrone isomer, giving rise to the first contraceptive pill Enovid®, containing 10 mg of noretinodrel and 150 µg of mestranol. In 1957, the Food and Drug Administration (FDA) approved the use of Enovid®, in an amount of 10 mg, for the treatment of menstrual disorders and, in 1960, for the purposes of contraception.

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The contraceptives initially available on the market were combined (containing in their composition an estrogen and progestogen component called with the acronym COC). A long road has been traveled from the FDA's approval of the first pill to the hormonal contraceptives currently available on the market. Ultimately, research led to reduced estrogen dosing due to harmful side effects.

The next step consisted in the introduction of new progestogens in order to reduce the androgenic effects caused by the progestogens of previous generations (AMERICAN, 2004, p. 520). In 1968, the first progestogen-only contraceptive (POC) was launched in France (GELIJNS, 1991, p. 172). The exclusion of the estrogen component favors some patients at risk, such as smokers over 35 years old and those with a history of thrombosis, hypertension or severe migraine. They are also indicated for the breastfeeding period because they affect neither milk production nor the child (AGULLES SIMÓ, 2015, p. 89).

Later, new estrogen-progestogen administration schemes were developed and alternative routes of administration were developed (DHONT, 2010, p. S14), to improve tolerance, convenience and compliance, including transdermal systems, implants and injectables (AMERICAN, 2004, p. 520).

Nowadays hormonal contraceptives are diffusely used for birth control and various therapeutic purposes, such as the treatment of polycystic ovary syndrome, dysmenorrhea, endometriosis and menstrual irregularities among others.

Of the four main mechanisms of action proposed for hormonal contraceptives, two can lead to embryo loss. One of these is prevention of implantation in the endometrium. The impediment results from a series of morphological changes that make the endometrium less receptive to this implantation. This effect occurs in all hormonal contraceptives, but particularly in the most recent ones, whose estrogen dose is decreased in order to reduce harmful side effects. Another mechanism of action that can lead to embryo loss results from the change in the motility of the fallopian tubes, which tends to delay or advance the arrival of a possible embryo in the uterus, so that it doesn't find it suitable for implantation.

This is a scoping review of previous studies, to estimate the prevalence of the occurrence of these post-fertilization effects in the convenience sample of previously studied women.

Methods

The first part of the investigation consisted in collecting data related to the mechanism of action of each of the three main classes of hormonal contraceptives available (combined contraceptives, progestin-only, hormonal IUD), and the different parameters and biological consequences associated with their use. Emergency contraception was not included in this analysis.

The literature review was performed employing the National Library of Medicine PubMed electronic database. The search terms selected were "combined oral contraceptive", "contraceptive efficacy", "contraception cervical mucus effect", "contraception

ovarian activity", "contraception effects endometrium", "contraception effects fallopian tube", "early pregnancy loss", "implant contraceptive", "infertility", "injectable contraceptive", "intrauterine device", "ovulation", "patch contraceptive", "post-fertilization", "progestin-only contraceptive".

Based on the scientific data collected, we estimated the probability of embryo loss caused by the use of each of the three categories of contraceptives under study.

Results

Mechanism of Action of Combined Contraceptives

COC are among the most used and studied pharmacological components. They contain exogenous estrogens and progestogens, in an orally active form (BAERWALD, PIERSON, 2004, p. 19). Traditionally, the main mechanism of action of COC was thought to be the inhibitory effect of progestogens, in the LH surge, while estrogens are necessary for endometrial stability, enabling a satisfactory bleeding pattern. Currently, the contraceptive effect is seen as the result of a wide variety of effects attributed to both, and may act at four levels with greater or lesser incidence, according to their combined action (HEUSDEN, 2002, p. 349):

1) In the hypothalamic-pituitary-ovarian axis, affecting the ovulatory process;
2) In the cervix, modifying the characteristics of the cervical mucus;
3) In the endometrium, making it inadequate to embryo implantation;
4) In the fallopian tubes, changing its motility.

Baerwald and Pierson mentioned a secondary inhibition effect on cervix dilation (DICKEY, 1997 apud BAERWALD, 2004, p. 20). Heusden and Fauser also reported a mechanism with a direct suppressive effect on the ovary (HEUSDEN; FAUSER, 2002, p. 349), which includes an inhibition of steroid biosynthesis in the ovary (ADEN; JUNG-HOFFMANN; KUHL, 1998, apud ELOMAA, 2001, p. 13). Of the four levels mentioned, contraceptive effectiveness results mainly from acting at level one (AGULLES SIMÓ, 2015, p. 75).

Hypothalamic-pituitary-ovarian axis

The hormones present in the contraceptives inhibit the normal activity of the hypothalamic-pituitary-ovarian axis (D'ARPE, 2016, p. 437; FLEISCHMAN, 2010, p. 750). The estrogenic component directly inhibits FSH secretion, limiting the development of the dominant ovulatory follicle. The progestagenic component strongly suppresses LH secretion, whose levels remain below those seen in the first days of the normal menstrual cycle, and which allow the growth of ovarian follicles. Therefore, there is no ovulation or production of pre-ovulatory hormones (estrogen and progesterone), and the endometrium is not prepared for the implantation of an eventually formed embryo (AGULLES SIMÓ, 2015, p. 75; MISHELL et al., 1977 apud WRIGHT; JOHNSON, 2008, p. 906).

At the ovarian level, there is a reduction in gonadotropin receptors, sensitive to their action (AGULLES SIMÓ, 2015, p. 75). Estrogen also intensifies the action of progesterone, which allows for a lower dose of these components and reduced side effects (KASTNER et al., 1990 apud WRIGHT; JOHNSON, 2008, p. 905).

Effectiveness of ovulation inhibition

Ovulation is understood as the release of a secondary oocyte from the graafian follicle (MEDICALDICTIONARY, 2021). Current science does not have unambiguous means to identify the occurrence of an ovulation. For this purpose, one can resort to two biochemical markers: βhCG and progesterone concentration in the mid-luteal phase period; two anatomical markers: direct visualization of the stigma of ovulation and serial sonographic visualization of the follicular rupture.

In any of these methods, false positives and negatives have been observed (HARRISON et al., 2018, p. 454). We will take a closer look at each of the mentioned ovulation identification means.

βhCG

The measurement of this hormone only permits to evaluate the implantation in the endometrium, not allowing to identify cases in which the embryo does not reach the implantation stage.

Concentration of progesterone in the mid-luteal phase period

After ovulation, LH values lead to the transformation of the follicular residue from which the egg is released into the corpus luteum, capable of producing estrogen and progesterone. Progesterone values at this stage have been used to identify corpus luteum formation due to ovulation. Authors such as Landgren, Unden, and Diczfalusy (1980 apud HARRISON et al., 2018), proposed a threshold value of progesterone that would be an indicator of the occurrence of ovulation. This value was defined as 13 nmol/L, since the progesterone values quantified in the plasma of 68 women, after presenting an LH peak, were higher than that value. However, these authors did not relate this concentration to other ovulation markers.

Several other limit values were proposed by different authors in order to identify ovulation occurrence, some of which were established in the context of ***in vitro*** fertilization experiments, only indicating that embryos do not survive as effectively below those values; they do not establish a correlation between luteal phase progesterone levels and documented egg release.

Several subsequent studies confirm that ovulation may occur with low levels of progesterone in the luteal phase. Birtch, Olatunbosun and Pierson (2006 apud HARRISON et al., p. 455, 2018) documented that in a case of administration of a combined oral contraceptive (30 µg EE/150 µg LNG) ovulation occurred in the presence of re-

duced levels of progesterone (0.79 ng/mL <=> 2.51 nmol/L) six days after ovulation (which would correspond to the period of highest progesterone level).

Croxatto et al. (1998 apud HARRISON et al., 2018, p. 455) reported that five of the nine cycles studied presented follicular rupture, but were considered to be anovulatory, due to the low levels of quantified progesterone. It is common to find this consideration in the literature based on arbitrary criteria of progesterone limits.

It is not clear that follicular ruptures correspond to ovulation events, as eggs can become trapped in the follicles which rupture in association with low progesterone production, although there is no scientific evidence for this. Likewise, there is no confirmation that a follicular rupture accompanied by low concentrations of progesterone cannot be followed by ovulation, and it is common to observe low concentrations of progesterone with the administration of hormonal contraceptives (HARRISON et al., 2018, p. 455).

Note that it is difficult to measure the concentration of progesterone in the luteal phase, as the corpus luteum releases this hormone in pulse mode, which causes fluctuations in blood concentration. Therefore, this premise must be taken into account, when analyzing published scientific studies that establish a minimum value of progesterone concentration that determines ovulation (FILICORI; BUTLER; CROWLEY, 1984 apud YOUNG, 2013, p. 6).

Visualization of the "ovulation stigma" by laparoscopy or laparotomy

Ovulation may be accompanied by a mark that remains on the surface of the ovary and is called "the stigma of ovulation" (SHAW, 1927 apud HARRISON et al., 2018, p. 455). Nevertheless, several studies revealed the occurrence of ovulation events that did not produce these stigmas (D'HOOGHE et al., 1996 apud HARRISON et al., 2018, p. 456; KATZ, 1988 apud HARRISON et al., 2018, p. 456). The fact that no stigma of ovulation are found does not ensure the absence of ovulation and the eventual formation of an embryo.

Observation of follicular rupture through ultrasonography

Regarding the ultrasound visualization, it was arbitrarily defined that a 50% reduction in follicle size would correspond to a follicular rupture, although this value has never been correlated with the actual occurrence of ovulation.

It is important to consider that, in order to reach the ultrasonographic criteria, there are conditioning elements such as the scanning frequency, the serial scanning time and the operator's skill. If the dominant follicle is not identified at the moment of its maximum dimension, the follicle can be considered to have undergone a reduction in size of less than 50%, being identified that situation as absence of follicular rupture, arbitrarily eliminating the possibility of ovulation, being only identified as LUF (luteinized unruptured follicle) (HARRISON et al., 2018, p. 456). Baerwald and Pierson

(2004, p. 20) pointed out that, due to the variability of the levels of sex hormones in the blood and the day of ovulation, efficient detection of ovulation occurrence may require frequent and comprehensive ultrasound and endocrinological evaluation. Therefore, the observation of follicular rupture via ultrasound cannot be considered a perfect technique for identifying ovulation. Some scientific data attest that the release of an egg can occur despite the arbitrary criteria defined for its identification via ultrasonography might not be met (LIUKKONEN et al., 1984 apud HARRISON et al., 2018, p. 456; CHECK et al., 1990 apud HARRISON et al., 2018, p. 456).

We can conclude that none of the current methods allows the unequivocal identification of a possible ovulation event. If the release of an egg is not accompanied by an increase in progesterone levels above the limit arbitrarily defined by the investigators, or if such release has not left a stigma on the ovary, or if the ultrasound has not identified the dominant follicle in the moment of its maximum dimension, the said release of the egg is not identified as ovulation. Consequently, the assessment of contraceptive effectiveness does not reflect reality, with the aggravating factor that an ovulation that occurs under the conditions of a deficient luteal phase (low levels of progesterone), and which is followed by fertilization, most likely causes the elimination of the embryo formed. For these cases, Harrison et al. suggested not to identify them as cases of "no ovulation occurrence", but rather cases of "no normal ovulation occurrence" (HARRISON et al., 2018, p. 456).

Hoogland criteria for determining ovulation occurrence

Hoogland and Skouby (1993 apud HARRISSON et al., 2018, p. 456) categorized the activity of the ovaries during the administration of hormonal contraceptives. For this purpose, they established categories defined according to a combination of markers such as: follicle size, evaluation of changes in follicle size by ultrasound and serum values of estradiol and progesterone (see annex A). One of the categories was defined as "ovulation" and the others as other stages of follicular development in which egg release may or may not occur, although these stages are not identified as "ovulation". The terminology and categorization adopted do not correspond to the definition of ovulation as the release of an egg from the ovarian follicle.

Different authors such as Check et al. (1990, apud HARRISSON et al., 2018, p. 457), Liukkonen et al. (1984 apud HARRISSON et al., 2018, p. 457), Croxatto et al. (1998 apud HARRISSON et al., 2018, p. 457), and Birtch, Olatunbosun and Pierson (2006 apud HARRISSON et al., 2018, p. 457), observed that the Hoogland criteria do not establish whether ovulation occurred or not, besides not contemplating other undefined ovulatory events (HARRISSON et al., 2018, p. 457). Liukkonen et al. (1984, p. 29), citing Smith et al. (1980), reported that it may not be possible to observe ovulation if, after the initial rupture, there is no collapse that leaves its mark, or when the collapsed follicle is filled with blood in a few hours. Nevertheless, several investigators adopted the Hoogland criteria as evidence for the occurrence or absence of ovulation

during the administration of hormonal contraceptives. This fact is surprising, since the authors themselves, Hoogland and Skouby (1993, p. 587), stated that, despite high concentrations of progesterone in the second half of the cycle and the presence of an LH peak in the middle of the cycle, being essential to prove the existence of residual ovarian activity, they are not sufficient, however, to distinguish between ovulation and the presence of luteinized unruptured follicles (LUF).

We now consider the effectiveness of COC at preventing ovulation. Harrison et al. (2018) published a systematic review of scientific articles in English, containing sonographic and endocrinological data on the activity of the ovaries, under the effect of the use of hormonal contraceptives. They categorized this data according to Hoogland's parameters. In the 17 studies analyzed, the vast majority of cases found were classified as active FLS (follicular like structure), in a percentage that varied between 1.9 and 67.4% of the cycles. Based on the Hoogland criteria, it is not possible to establish how many follicles actually rupture. However, follicular rupture with active FLS can occur (HARRISSON et al., 2018, p. 459), with the aggravating factor of being followed by deficient progesterone concentration in the luteal phase, which results in insufficient preparation of the endometrium for implantation of the embryo and inadequate support for the development of pregnancy, leading to the loss of the embryo.

Harrison et al. (2018, p. 458) referred that researchers like Lawrenz, et al. (2018), Devoto et al. (2009), Ozlu et al. (2012), Arce et al. (2011), Andersen and Andersen (2014), Kaur and Gupta (2016), evaluated the impact of "dysfunctional ovulation"[1] on embryo survival, concluding that low levels of progesterone in the middle luteal phase (without setting a limit value) are associated with considerable embryonic loss (ARCE et al. 2011 apud HARRISON et al., 2018, p. 458).

Several studies documented the occurrence of follicular rupture during treatment with hormonal contraceptives, followed by inadequate progesterone concentration in the luteal phase. Among these researches, we highlight: Djuikers et al. (2015, p. 425 apud HARRISON et al., 2018, p. 459), Ludicke et al. (2001, p. 245 apud HARRISON et al., 2018, p. 459), and Birtch, Olatunbosun and Pierson (2006, p. 239 apud HARRISON et al., 2018, p. 464). This latest study also revealed that, even after the discontinuation of the contraceptive administration, 40% of cases were observed in which ovulation was accompanied by abnormal progesterone concentrations.

Other studies have revealed the occurrence of follicular rupture with the characteristics defined for "dysfunctional ovulation" in 71% of cases, compared to 9% in controls (CROXATTO et al., 2006 apud HARRISON, 2018, p. 464). Croxatto et al. (1998 apud HARRISON, 20018, p. 464) identified follicular rupture in 30% of the

[1] Defined by the authors as follicular ruptures not preceded by an LH peak or in which its values are below 21 IU/L, or not being followed by an increase in serum progesterone concentration beyond 12 nmol/L, which may correspond to any of the Hoogland categories. The attenuated LH peak is common in cycles when using hormonal contraceptives (Endrikat et al., 2013; Van Heusden; Coelingh; Fauser, 2002; Seidman et al., 2015; Kroll et al., 2015). These studies are cited by Harrison et al. (2018, p. 458).

studied cases, after the administration of mifepristone and nomegestrol. However, as five of these ruptures presented low progesterone production, they were considered non-ovulatory (similar to the Hoogland criteria).

Harrison et al. (2018, p. 465) theorized that the most common scenario observed with the use of hormonal contraceptives is that of follicular rupture accompanied by inadequate progesterone production in the luteal phase, since in the review presented, the occurrence of such ovulatory states is observed in a percentage ranging from 1.9 to 67.4% of the cycles studied. Hoogland's terminology, adopted by a large number of researchers, assesses contraceptive efficacy regardless of follicle rupture and egg release, since suboptimal progesterone values can contribute to the "contraceptive" effect by eliminating embryos. The published contraceptive efficacy values correspond only to the embryos that have implanted successfully, regardless of the luteal phase conditions, and do not include embryos that once fertilized may have been eliminated by deficient luteal phase conditions that prevented implantation. The published efficacy represents the minimum possible number of embryos created. In the opinion of Harrison et al. (2018, p. 466), it would be necessary to develop an ovulation identification method that has a practically zero percentage of false negatives, in order to ensure that the contraceptive works only by mechanisms of action before fertilization.

Milsom and Korver (2008, p. 244) also published an article that consists of a review of research on the incidence of ovulation through the use of oral contraceptives. As Harrison et al. (2018) stated, Milsom and Korver indicated that many of the studies carried out are based on inadequate methodology and/or criteria, and in many cases, measurements were not taken on the most critical days to identify the occurrence of ovulation. In fact, in some studies, no measurements of serum progesterone levels have been made; in other cases, the frequency and duration of scanning were inadequate, which is confirmed by the occurrence of a pregnancy in the research presented by Teichman et al. (1995), although the respective ovulation was not identified, as they did not visualize any ruptured follicles. This pregnancy could not be explained by pill intake forgetting or drug interaction.

Citing Qeenan et al. (1980), Milsom and Korver (2008, p. 244) also discussed that the interpretation of ultrasonographic results is ambiguous, even in physiological menstrual cycles, because of the wide variety of dimensions of pre-ovulatory follicles, and several aspects of the corpus luteum formed. Therefore, the use of follicular diameter as the sole criterion of ovulation is not the most suitable, since the situation is complicated by the intake of hormonal contraceptives that alter folliculogenesis and generate multiple follicles.

Regarding ultrasonography, d'Arpe et al. (2016, p. 439) mentioned a study (JOKUBKIENE; SLADKEVICIUS; VALENTIN, 2012) that demonstrates the great variability resulting from sonographic observation in 2D, 3D or Doppler, in women using COC.

Milsom and Korver also report that many studies included a small number of participants, and the duration of the study and the interpretation of results was quite

varied as to the definition of ovulation and the bioanalytical and statistical methods adopted. The authors also identified a lack of relevant information that would allow a better understanding of the results.

Studies involving EE (ethinyl estradiol) doses between 30-35 µg/mL showed a percentage of ovulation (per individual) that varied between 0 and 30%. The authors did not count as ovulation the pregnancy that occurred in the study presented by Teichman et al. (1995).

Studies involving EE doses between 15-20 µg/mL showed an ovulation percentage that varied between 0 and 28%. It should be noted that, for example, in the study carried out by Rossmanith, Steffens and Schramm (1997, p. 439), the authors stated that, although ovulation events were not observed in any of the cycles, based on the ultrasound parameters obtained and in hormonal concentrations, 4.15% of the cycles investigated in group a) and 2.9% in group b) presented progesterone concentration values above 5 nmol/L. This might indicate that, presumably, ovulation would have occurred, although in the results tables these data are not indicated as ovulation occurrence.

Studies with administration mode with phases (bi and three-phase) showed a percentage of ovulation that varied between 0 and 50%. In the set of studies carried out, ovulation events were observed with all types of combination of progestogenic component.

Baerwal and Pierson (2004, p.20) reviewed 29 studies, 6 of which are included in Milsom and Korver (2008). Of these 29 studies, 10 documented ovulation in oral contraceptives users. In 2 of the 29 studies, two pregnancies were observed, although the respective ovulation was not detected. One of these cases, the one reported by Teichmann et al. (1995), had already been mentioned by Milsom and Korver (2008). The other case concerns a study developed by Young et al. (1992, p. 679). According to Baerwald and Pierson (2004, p. 19), it is still unknown why some follicles ovulate and others regress or form anovulatory follicular cysts.

Agulles Simó (2015) also mentions, for example, the following ovulation rates obtained experimentally 4-10% (HILGERS, 1994), 4.7% (VAN DER VANGE, 1984) and 10% (CHOWDHURY et al., 1980). In the latter case, the occurrence of ovulation was defined considering a progesterone concentration greater than 4 ng/mL (less perfect way of identifying the occurrence of ovulation).

It is possible to conclude, from the analysis of the results presented above, that ovarian follicular development is not totally inhibited during the use of combined oral contraceptives (VAN HEUSDEN; FAUSER, 2002; PIERSON et al., 2003 apud BAERWALD; PIERSON, 2004; RABE; NITSCHE; RUNNEBAUM, 1997)[2]. Several factors

[2] Regarding patches and rings, they allow for more uniform levels of estrogen and progesterone, giving rise to an activity in the ovaries similar to or less than that caused by oral contraceptives. A study on NuvaRing®, concluded that it had a similar effect of suppressing ovarian activity compared to a combined oral contraceptive (DUIJKERS et al., 2004, p. 2668; ODDSON et al., 2005, p 176). A comparative study of the efficacy of ovulatory inhibition between the Ortho Evra patch and a combined oral contraceptive, showed that the COC had greater ovulatory inhibition effects (PIERSON et al., 2003, p. 34).

might influence the inhibitory efficacy of hormonal contraceptives, which can cause a decrease in the concentration of active contraceptive compounds in the serum, favoring the occurrence of ovulation. Follicular suppression is related to the dose and type of the progestogenic component (GRIMES et al., 1994 apud RABE; NITSCHE; RUNNEBAUM, 1997, p. 48) but more so to the estrogen dose (SPELLACY, 1980; FAUSER; HEUSDEN, 1997). Follicular development is also influenced by the day of the cycle when the contraceptive intake begins (KILLICK; EYONG; ELSTEIN, 1987, p. 412). The delay appears to make the hypothalamic-pituitary axis less susceptible to inhibition.

Extension of the break period can also diminish the anovulation efficacy of COCs. During the pause period of oral contraceptive ingestion, follicular development occurs (KILLICK, 1989, p. 580; RABE; NITSCHE; RUNNEBAUM, 1997, p. 39). Dominant follicles with a diameter greater than 10 mm can develop, and their subsequent development is even observed with the resumption of the contraceptive (VAN HEUSDEN, BENNINK, FAUSER, 2002, p.509; SULLIVAN et al., 1999, p. 119).

If the contraceptive intake is forgotten, the ovulation inhibitory efficacy may decrease, as observed in some studies (RABE; NITSCHE; RUNNEBAUM, 1997, p. 39), and follicular rupture may occur if the omission happens at a time when the follicle is in the development stage (KILLICK, 1989 p. 582; KORVER; GOORISSEN; GUILLEBAUD, 1995 apud RABE; NITSCHE; RUNNEBAUM, 1997, p. 48).

Age can affect ovulation inhibitory efficacy. Larger and more numerous follicles were identified in users aged 20-29 years compared to those aged 30-39 years (JOKUBKIENE; SLADKEVICIUS; VALENTIN, 2012, p. 261). It also depends on drug interactions (LEE, 2009, p. 26) and the occurrence of vomiting.

Alteration of the cervical mucus characteristics

The cervical mucus changes according to the concentration of estrogenic and progestogenic components in COCs, mimicking what happens during the progestational phase (post ovulation) in a normal cycle and during pregnancy. But are changes in hormone concentrations, resulting from the use of hormonal contraceptives, sufficient to prevent the migration of sperm from the cervix into its interior and into the fallopian tubes (KESSERU-KOOS, 1971, p. 584)? The effect of mucus changing characteristics depends on the dose. Only a constant serum level of progesterone (which in practice is not observed), can ensure the barrier to the passage of sperm. A chronic inhibition of the cervical mucosa can cause its atrophy, absence of mucus production and the consequent disappearance of the barrier (DI PIETRO; MINACORI, 1996, p. 868).

According to Han, Taub, and Jensen (2017, p. 310), although the characteristics of cervical mucus change radically in response to both natural and artificial hormonal concentrations, there is still insufficient experimental evidence to support the mucus contraceptive effect. The techniques commonly used to assess the characteristics of

Another study on a patch containing ethinyl estradiol and gestodene showed satisfactory inhibitory efficacy (HEGER-MAHN, 2004, p. 173).

cervical mucus (Insler score, post-coitus test and sperm penetration capacity), were developed to assess infertility and not to discriminate changes in cervical mucus under the effect of contraceptives. Even for the purposes they have been developed, they have not been shown to be useful (HAN; TAUB; JENSEN, 2017, p. 314). In addition, the quality of the mucus can be altered as a result of infections, injuries, previous surgeries, anti-sperm antibodies and inadequate periodicity in the collection of mucus samples (HAN; TAUB; JENSEN, 2017, p. 314).

The present analysis of possible changes in the quality of cervical mucus, requires that some relevant elements be considered. In particular, attention should be paid to the difficulty in identifying changes in cervical mucus, due to the high sensitivity of the uterine cervix to hormonal variations, even in a cycle in which hormonal contraception is not used. The effect depends essentially on the type and dose of progesterone contained in the contraceptive. It is known that serum progestogen levels fluctuate, so the quality of mucus can vary within 48 hours (DI PIETRO; MINACORI, 1996, p. 877). In a study published by Ulstein and Myklebust (1982, p. 49), regarding the administration of a combined oral contraceptive, the analysis of cervical mucus showed good sperm penetrability, right after the pill was stopped and before the first menstrual loss.

The multiplicity of techniques used in studies on the influence of contraceptive agents on the ability of sperm penetration, has given rise to divergent results. Some authors found changes in this capacity, others did not (KESSERU-KOOS, 1971, p. 601). In addition to this, there is also the diversity in the bioanalytical and statistical methods. In the case of COCs, we should also consider the fact that few studies have been done.

Here we present some of the results obtained in the case of combined contraceptives. In a study of 118 volunteers, Rossmanith, Steffens and Schrammt (1997) compared the effect of administering two combined oral contraceptives on the quality of cervical mucus, and they observed that both contraceptives caused similar effects. They found that more than 95% of the cycles analyzed had cervical mucus of minimal quality and claimed, based on these data, that the permeability of mucus to sperm was also minimal. It should be noted that the study was not accompanied by any control and no tests involving sperm were performed.

Steward et al. (2012) compared the quality of cervical mucus using a COC in two regimens. Sampling was done in the middle of the cycle and on the last day of the break period. The results revealed a decrease in the quality of the cervical mucus, expressed in terms of average score, from 9 to 1, according to a scoring system validated in previous studies by correlation with subsequent pregnancies. A score of 9 was "excellent," a score of 7 or 8 was "good," and a score less than 7 was considered "poor." The authors qualified the mucus as a barrier for the penetration of sperm, preventing fertilization, even with ovulation occurrence. However, in the days of mucus sampling, the measurement of the formed ovarian follicles was not included. In one of the analyzed regimes, 3 of the 18 volunteers had excellent or good sperm penetrability in one of the samples and 2 of the 18 in another sample.

Spona et al. (2008) evaluated the effects of a COC on 33 volunteers, for which the amount and consistency of cervical mucus (cervical reaction score) was assessed. Results were classified as negative (score 1–3), slight (score 4–6), moderate (score 7–9) or full reaction (score 10–12). Sampling was performed on alternate days. The quality of the mucus was classified as negative (score 1-3), so that the authors claimed unfavorable conditions for fertilization. No tests involving sperm were performed.

Di Pietro and Minacori (1996, p. 876-877) referred to the study done by Widholm and Alapiessa (1977) in 4 users of a COC, in which 9 samples out of 12 (75%) showed mucus with impenetrable quality to sperm.

Regarding the published results, note that not all analyses were accompanied by an assessment of hormone levels nor ovulation identifiers. This is problematic because the increase in estrogen levels associated with ovulation can alter the characteristics of the cervical mucus, reducing its blocking ability to sperm permeability. In addition, the frequency of sampling is quite varied from study to study and not always in the most relevant periods. Not all of them present an evaluation of the sperm penetration capacity in the endometrium (through post-coitus aspiration) which is considered by some authors to be of high importance (KLEEGMAN; KAUFMAN, 1966 apud ROLAND, 1970, p. 215).

We should also note that the values presented are absolute or relative to the cycles, the most significant being values that establish a ratio between the number of sperm steps and the total number of sexual intercourse in a given period of time and the moment in which this happens, establishing a distinction between the period of ingestion of the contraceptive and the period of pause (AGULLES SIMÓ, 2015, p. 76).

It is also considered that, in most experiments, mucus was collected from the cervix and in some the endometrium was aspirated. However, Kunz et al. (1996 apud PECK et al., 2016, p. 40) stated that the sperm goes preferentially to the tube located on the same side as the ovary, where the formation of the dominant follicle occurs, suggesting that there will be a preferential accumulation in the fertilization site. Suarez and Pacey (2006 apud PECK et al., 2016, p. 40) claim that the main functional human sperm reservoir is found in the fallopian tubes.

Despite some results indicating the possibility of a barrier effect on the part of the cervical mucus, when administering a COC, according to Dunson (2001 apud Endrikat et al., 2013, p. 233), a scarce or absent mucus may not necessarily prevent a pregnancy. Also Faundes et al. (1981, apud BRACHE et al. 1985, p. 273) proved that low-quality results of cervical mucus do not exclude the transport of sperm to the fallopian tubes.

In addition to the considerations mentioned above, Eggert-Kruse et al. (1989 apud HAN; TAUB; JENSEN, 2017, p. 314) concluded that the ability of the sperm to penetrate the cervical mucus depends more on the functional competence of the sperm than on the quality of the cervical mucus itself. Further investigation is needed to clarify the role of cervical mucus in current hormonal contraceptives (HAN; TAUB; JENSEN, 2017, p. 310).

Uterine endometrium alteration

The ability of the endometrium to allow a normal implantation of the embryo is called "receptivity". Optimal receptivity leads to normal implantation processes, which are the basis for a healthy pregnancy (LESSEY; YOUNG, 2019, p. 611).

The implantation process of the embryo in the womb is complex. It involves biochemical communication ("cross-talk") between the embryo and the mother's endometrial cells, in order to ensure that the optimal conditions are established so that the embryo can implant itself when it reaches the uterus. This biochemical communication is conditioned by the preparation of the endometrium by estrogen and progesterone, which is established in a precise period of time and through determined concentrations of the mentioned hormones (ACHACHE; REVEL, 2006). In addition to the time and the exact amount of hormones, the endometrium has to respond adequately to them (RIESEWIJK et al., 2003; CASTRO-RENDÓN et al., 2006).

An effective implantation also depends on the role of integrins, which are cell adhesion molecules present on the surface of the endometrium and in the formed embryo. The implantation window corresponds to the brief interval between days 20-24 of the cycle, during which specific integrins are co-expressed (LESSEY et al., 1994 apud SOMKUTI; FRITZ, 1996). Somkuti et al. (1996) showed that the gene expression of integrins is strongly altered in users of oral contraceptives. However, no articles were found in which the effect of ingesting oral contraceptives on the expression of integrins in situations of ovulation has been evaluated.

Wilcox et al. (1999 apud FOX, 2016, p. 874) noted that implantations that occur beyond the implantation window (between days 20-24 of the cycle), have a greater probability of embryo loss. The synthetic estrogens and progestogens, contained in combined contraceptives, have the same biological effect on the endometrium as their natural counterparts. During their use, the production of these compounds by the ovaries decreases and changes in the endometrium occur in response to exogenous hormonal administration (RIVERA; YACOBSON; GRIMES, 1999, p. 1264).

The effect of the progestogenic agent takes precedence over the estrogenic component, unless its concentration is very high (COMITATO SCIENTIFICO, 2020, p. 3), inhibiting the normal proliferative changes developed by estrogen, and leading to thinning, spaced, and atrophied glands (AREF et al., 1973; SOMKUTI et al., 1996 apud LARIMORE, STANFORD, 2000, p. 128), almost nonexistent vascularization and transient and incomplete decidualization or secretory transformation (AGULLES SIMÓ, 2015 , p. 66), with modification of the biochemical and protein composition of the endometrium (UMAPATHYSIVAM; JONES, 1980 apud LARIMORE, STANFORD, 2000, p. 128). In most cases, the endometrium becomes thinner (MOGHISSI; MARKS, 1971 apud RIVERA; YACOBSON; GRIMES, 1999, p. 1265).

Rabe, Nitsche and Runnebaum (1997, p. 39) compared the effects of 7 COC formulations on ovary function and thickness of the endometrium. With each formulation, a significantly thinner endometrial thickness was observed than in the controls. The

results obtained reveal the strong progestogenic effect of monophasic compositions (desogestrel DSG/ethinyl estradiol EE and levonorgestrel LNG/ethinyl estradiol EE). In preparations with a low progestogen dominion, endometrial growth has been observed; in this study, this fact was confirmed by the observation of the lesser suppressive effect caused by compounds containing norgestimate. These also have a higher concentration of estrogen, which may have contributed to the development of the endometrium. The authors refer that the observation of the endometrium of women who use oral contraceptives revealed that these interfere with its maturation, and may prevent the implantation of the blastocyst (RABE; NITSCHE; RUNNEBAUM 1997, p. 9).

In addition to the aforementioned research, several studies were carried out with COC and revealed that their use leads to the transformation of the endometrium from a proliferative state to a secretory or inactive state, in a high percentage of users, with the consequent decrease in the average thickness of the endometrium. Such studies include, for example, Rabe et al. (2010), Spona et al. (1997), Rossmanith, Steffens and Schramm (1997) and Endrikat et al. (2013).

The effects on the endometrium are attributed to the action of synthetic progestogens, but also to the reduction of follicular production of steroids. Some authors claim that even in the presence of some residual follicular activity, profound anti-conceptive effects were observed in the cervix and in the endometrium, contributing to contraceptive efficacy. A thin or atrophied endometrium, or with incomplete secretory transformation becomes an inadequate environment for embryo implantation (CHWALISZ et al., 2006 apud RABE et al., 2010, p. 362).

During the follicular phase of natural menstrual cycles, the thickness of the endometrium increases under the influence of estrogen stimulation. While some studies suggest no relationship between cycle phase and endometrial thickness (Fleischer et al., 1986; Ueno et al., 1991), IVF implantation rates are better when the thickness is greater than 5-10mm (GLISSANT; DE MOUZON; FRYDMAN, 1985; GONEN et al., 1991 apud ABDALLA et al., 1994, p. 365; NOYES et al., 1995; RICHTER et al., 2007; KOVACS et al., 2003 apud REVEL, 2012, p. 1029; ISAACS et al., 1996; CHEN et al., 2010; AL-GHAMDI et al., 2008 apud REVEL, 2012, p. 1029). The thicknesses observed in researches with users of hormonal contraceptives are generally less than 8 mm, with examples of 7 mm (ENDRIKAT et al., 2013), 5 mm and 4 mm (RABE et al., 2010), 2,9 mm (VAN DEN BOSCH et al., 2002) or lower.

Some authors, despite confirming that hormonal contraceptive methods, particularly low-dose progestogens, cause effects on the endometrium, which theoretically could affect the embryo implantation, claim, however, that there is no scientific evidence that implantation prevention is really a consequence of the contraceptive use (RIVERA; YACOBSON; GRIMES, 1999, p. 1263).

It may also happen that, although implantation occurs, the endometrium does not present a structure capable of ensuring pregnancy. Some authors argue that, despite different companies that produce hormonal contraceptives and scientific publications claim that the effects caused by contraceptives on the endometrium contribute to their

contraceptive efficacy (AGULLES SIMÓ, 2015, p. 77), the hormonal production of the corpus luteum and follicle prepare the endometrium for proper implantation.

However, as discussed above, ovulation accompanied by a deficient luteal phase (low progesterone concentrations) have been observed, resulting in insufficient preparation of the endometrium for implantation of the embryo and inadequate support for the development of pregnancy, causing potential embryo loss. Consider also the investigation carried out by Chowdhury et al. (1980, p. 241), previously mentioned, in which they assessed the occurrence of escape ovulation events in cases of forgotten ingestion of a combined low-dose hormonal contraceptive. The results obtained indicated the occurrence of ovulation in 10 of 35 women in the first treatment cycle and in 5 of 19 in the third treatment cycle. However, in the entire studied population, the endometrium did not manifest any secretory effect (remaining atrophic). The authors state that, although forgetfulness of intake has caused escape ovulation in some users, the pharmacological effects of the contraceptive on the endometrium and on the cervical mucus may continue to provide contraceptive protection, although they do not comment on the degree of this protection (p. 246). Thus, the argument presented regarding the impossibility of the existence of an "unfit" endometrium for implantation lacks scientific foundation, at least based on these studies.

An article from Baerwald et al., (2006) is sometimes used to disprove endometrial atrophy as a mechanism for clinical pregnancy prevention, when ovulation occurs despite the use of hormonal contraceptives. This study cannot rule out this mechanism, as it deals with a research done with non-daily users of hormonal contraceptives. The contraceptive intake was made during periods of the cycle when the ovarian follicles measured 10 mm, 14 mm or 18 mm, situations in which the proliferative phase of the endometrium was no longer as susceptible to an alteration that would compromise the implantation of an embryo.

The changes caused in the endometrium may persist for some time even after the contraceptive suspension, as evidenced in the scientific literature and cause embryo loss in long-term users of contraceptives (NASSARALLA et al., 2011), (GARCÍA-ENGUÍDANOS et al., 2005).

Studies conducted with women who interrupted the use of contraceptives, reveal that it takes more than a month for menstruation to return to normal. Menstruation shows the ability of the endometrium to develop its usual thickness. If it doesn't return to normal after the discontinuation of the contraceptive, it will be even less likely to return if administration continues, even if ovulation occurs (MIRKES, 2002, p. 14).

Rice-Wray et al. (1967 apud DI PIETRO; MINACORI, 1996, p. 879) observed the occurrence of ovulation in 77% of women in the first treatment cycle (about 35 days) without administration of an oral combined contraceptive. In 15% of women, ovulation was observed only in the second cycle without treatment, and in 3% only in the third. Endometrial biopsies were performed in the last 15 days of the first cycle without treatment. Only in 57% of the cases in which ovulation had occurred, the endometrium was of the secretory type, and in the remaining 27% it was atrophic. This means the recovery

of the endometrium requires a considerable time, greater than the temporal window that precedes implantation in a cycle.

There is no standard method of measuring endometrial receptivity, which allows the evaluation of its function outside a conceptive cycle. The establishment of reliable methods for assessing receptivity depends on the validation of biomarkers of the endometrium, for which further studies are required (LESSEY, 2011, p. 522).

There are those who claim that an adequate endometrium is not necessary for the implantation to be effective, since there are implantations that take place in the fallopian tubes, giving rise to ectopic pregnancy, caused by integrins in the tubes (AGULLES SIMÓ, 2015, p. 78). In either case the consequence will always be the death of the embryo and a risk to the death of the mother.

Some authors claim the occurrence of implantation in altered endometrium, which in fact happens, since the percentage of unwanted pregnancies is not null. However, the probability of survival of an embryo is greater when it is implanted in a functional and morphologically adequate endometrium, than in one that does not present the ideal conditions, because of modifications caused by the contraceptive intake (ALCORN, 2011, p. 87).

Fallopian Tubes

After fertilization, the embryo is directed to the uterus, traversing the fallopian tubes, through the movement of peristalsis (movement, caused by sequential muscle contraction) and cilia that also strike towards the uterus, facilitating the progression of the embryo. Through that period of time, the endometrium must be prepared to "host" the embryo.

The movements of the cilia depend on the amount of progesterone in circulation. POCs interfere in these processes (MCCANN; POTTER. 1994, p. S20) as they cause a delay in movement, so that the embryo can reach the uterus in a period of time that is beyond the optimal implantation window, compromising it (WANGGREN et al., 2008; MAHMOOD et al., 1998 apud ZHANG et al., 2015). It may also happen that the embryo ends up implanting itself in the fallopian tubes (ectopic pregnancy), as previously mentioned.

Larimore and Stanford (2000, p. 127) established an interesting reasoning: if the action of the combined contraceptives in the fallopian tubes and endometrium did not cause any post-fertilization effect, then the reduction in the rate of intrauterine pregnancy in the users of these contraceptives , would be proportional to the reduction in the rate of extrauterine pregnancy (e.g. ectopic) in women using the same contraceptives. As the effect of using these is to increase the extra-uterine pregnancy vs. intrauterine, this indicates that one or more post-fertilization effects exert their action through the use of these contraceptives. The authors presented bibliographic references indicating the increase in this relationship, among which Job-Spira et al. (1990), with a ratio of 4.3 and Thorburn et al., (1986) with a ratio of 4.5. The results correspond to two studies carried out in 7 maternity hospitals in France and 3 in Sweden, involving 484 women

with ectopic pregnancies and 289 controls of pregnant women. They suggest that at least some protection against intrauterine pregnancy is possible via post-fertilization effects (among which is ectopic pregnancy).

The effect of COC on the fallopian tubes can also include an acceleration of the cilia beating and peristalsis, which would cause the embryo to reach the uterus before the optimal implantation period. This beating alteration might also work as an obstacle to the passage of sperm and their nutrition (AGULLES SIMÓ, 2015, p. 79).

Mechanism of Action of Progestin Only Contraceptives

The mechanisms of action, previously described for combined contraceptives, are those that are also observed with progestin only contraceptives, although the incidence of one or the other mechanism varies according to the type of contraceptive. These compounds do not present estrogen in their composition and do not benefit from the reinforcement of their action, as in combined contraceptives. The absence of estrogen causes a reduction in the ovulation inhibition effect (DI PIETRO; SGRECCIA, 1988, p. 9). In addition, its concentration in progestogenic content is lower than that of combined contraceptives.

Effectiveness of ovulation inhibition

According to information published by the ESHRE Capri Workshop Group (2001, p. 1532), between 10-15% of POP (progestin-only pill) users will experience complete inhibition of ovarian activity. About 50% tends to have regular ovulatory cycles with a normal luteal phase. About 35-40% present inconsistent suppression of ovarian activity with varied follicular development and eventual ovulation with inadequate luteal phase.

McCann and Potter (1994, p. S13) reported that inhibition of ovulation occurs in 50% of cycles. According to Kim-Bjorklund, Landgren and Johannisson (1991 apud RIVIERA; YACOBSON; GRIMES, 1999, p. 1264), ovulation occurs in approximately 40% of POP users, and there are also cases in which follicular activity occurs without development of the corpus luteum or with signs of insufficient luteal phase and in some users ovarian function is completely suppressed.

In their review of scientific articles on the occurrence of ovulation in users of oral contraceptives, Milsom and Korver (2008), mentioned that the percentages of ovulation (per subject), obtained in experiments on users of progestogens vary between 28.6% and 39.5% in the case of norethisterone between 28.1% and 65.5% in the case of levonorgestrel, and 0% and 3.4% in the case of desogestrel. Recall the fact that the authors mentioned that, in many studies, inadequate ovulation methodologies and definition criteria were used.

In a comparative study of the use of desogestrel and drospirenone, Duijkers et al. (2015) referred to greater efficacy of desogestrel, compared to other POPs, with ovulation rates of 1-2% (RICE et al., 1999 apud DUIJKERS et al., 2015, p. 2). Harrison et al. (2018) found that most situations of ovarian activity, in POP users were active follicle like structures FLS. In particular, 42.6% and 60.3% of cases of active FLS were

identified with drospirenone and desogestrel, respectively. In an evaluative study on the use of dienogest, 17.4% to 67.4% of cases were identified as FLS (KLIPPING et al., 2012). The article also presents the observed values of ovulation and LUF according to the Hoogland criteria, identified in each of the referred studies.

In the case of injectables, DMPA (medroxyprogesterone acetate), contained, for example, in Depo-Provera®, is quite effective in inhibiting ovulation. In the study developed by Petta et al. (1998a, p. 817) ovulation was observed in 30% of participants. Ovulatory cases were relative to injections given between days 11-13 of the menstrual cycle and one on day 10. There were no ovulation events in cases where the injection was administered between days 8 and 9, although one case in day 9 had follicle rupture (reduced in size by ≥ 50% after reaching a diameter of 15 mm) not identified as ovulation because the progesterone levels were inferior to 2.5 ng/mL. Note that criteria used to define ovulation occurrence was different from Hoogland's (reduction of follicle from 13 mm and progesterone level superior to 1.6 ng/mL). Bassol et al., (1984), affirmed total inhibition of ovulation after injection with DMPA. The return of follicular activity preceded that of luteal function in all subjects; however, there were a number of cases of follicular activity without evidence of subsequent luteal function (BASSOL et al., 1984). This means that ovulation events can occur in a situation of deficient luteal phase. These authors defined the existence of follicular and luteal activity by means of an increase in serum estradiol levels above 150 pg/mL and an increase in serum progesterone concentrations above 3 ng/mL, with no ultrasound analyzes performed.

In the case of implants, users of levonorgestrel (Norplant®)[3] experienced ovulation in 10% of cycles in the first year, and in the fifth year the percentage varies between 30 and 75% (FAUNDES et al., 1991 apud RIVERA; YACOBSON; GRIMES, 1999, p. 1265). However, progesterone production in the ovaries is low and causes a luteal phase defect, which may be at least partially responsible for the contraceptive effect in the case of women who ovulate (BRACHE et al., 1985 p. 270). Croxatto (2002, p. 22) states that about one third of the cycles can be characterized by ovulatory dysfunctions such as LUF.

With the etonogestrel implant (Implanon), 4 ovulation events were observed in 523 cycles analyzed. It is considered that ovarian suppression corresponds to 99% of the contraceptive efficacy of the implant (CROXATTO p. 24, 2002). With nestorone, 6%, 24% and 37% of ovulatory cycles were observed at 12, 18 and 24 months of use in users of an implant and 6% at the end of 24 months, in those who used two implants (CROXATTO, 2002, p. 24).

With nomegestrol acetate (Uniplant®), 36% of cycles were without follicular development, 15% had persistent follicles, 29% had follicular cysts and 20% had follicular ruptures; none, however, before 6 months (CROXATTO, 2002, p. 24).

[3] Although Norplant® was withdrawn from the market its data are useful. The main difference from Norplant II (Jadelle®) is the number of capsules and time of use (BRACHE et al. 2006).

Progestogen implants are more effective than oral contraceptives in preventing ovulation because they avoid errors caused by ingestion forgetting or delay in it (MECKSTROTH; DARNEY, 2001 apud SULLIVAN, 2006, p. 192).

The literature shows that combined oral contraceptives and progestogen desogestrel are equally effective in inhibiting ovulation, whereas other progestogen formulations are less effective (MILSOM, KORVER, 2008, p. 237). However, the proportion of FLS found in the case of desogestrel, published by Harrison et al. (2018), was very high and in conditions of deficient luteal phase, similar to what we saw in the case of COC. Therefore, it is possible that there may be ovulation events in conditions that endanger the embryo's survival.

Alteration of the cervical mucus characteristics

Petta, Faundes and Dunson (1998b) reported the effects of administering Depo-Provera®. After 24 hours of administration, the quality of the mucus was, by them, identified as being poor in about 90% of the users. Measured the sperm penetration capacity in vitro, it corresponded to a value of less than 1 cm, in 87% of users. Three days after the injection, with the exception of one user, all had poor mucus quality (97%). In the mentioned user, the occurrence of an ovulation was identified and the sperm penetration capacity was maximum. The authors warn of the fact that the confidence limits were large and only 30 participants were included in the study, with only 7 presenting a good quality of mucus before the administration of the contraceptive.

An article that reports the contraceptive action of progestogenic implants (CROXATTO, 2002) stated that in 34 users of Norplant®, whose post-coital cervical mucus sampling was performed on days 10 to 19 of the cycle, sperm was found without mobility or absent, in about 90% of the samples. Two cases of cervical mucus permeable to sperm were found.

In another study with LNG implant, in 31% of users the mucus was very viscous and thick and, in 69%, the distance covered by the avant-garde sperm was less than 0.5-2 cm (BRACHE et al., 1985 apud CROXATTO, 2002, p. 23).

Another study looked at cervical mucus samples in the case of a Norplant® implant. Three days after insertion, low quality of mucus was found in 80% of users (DUNSON et al., 1998 apud CROXATTO, 2002, p. 23).

Davies et al. (1993) identified negative sperm penetration tests throughout a study of an implant releasing 3-ketodesogestrel. Only in one woman was sperm penetration seen.

According to Martinez-Manautou et al. (1967, p. 731-732) in an in vivo test to assess post-coitus sperm penetration, performed on women using chlormadinone acetate, 80% had little or no sperm penetration. The authors stated that it is not possible to be sure whether changes in cervical mucus are functionally important without demonstrating the prevention of sperm penetration.

Moghissi and Marks (1971, p. 429), in their study on the effect of administering norgestrel in microdose, on cervical mucus, reported only one occasion (in six users), of sperm penetration in cervical mucus. They stated that the cases in which the highest penetration of sperm was found were those that coincided with higher concentrations of estrogen in the serum. This fact can be related to the possibility that, in the event of an ovulation, the peak of estradiol may alter the mucus' ability to act as a barrier to the passage of sperm, improving the characteristics of the mucus. However, the time required for this effect and the degree of it are unknown (BEVINGTON; DI SILVESTRO, 2003, p. 80).

Regarding the changes that the mucus may undergo, caused by a possible ovulation due to failure of the method, it should be noted that in the experiment developed by Kesseru-Koos (1971, p. 600), with norgestrel, there was an almost total absence of sperm in the uterine cavity, with some exceptions that presented a small amount of it. In one of these cases, a pregnancy occurred due to failure of the contraceptive method. Regarding the fact that no sperm was found in the uterine cavity, it should also be borne in mind that, as previously mentioned in relation to COC, spermatozoa are preferentially directed to the fallopian tube located on the same side as the ovary, where dominant follicle formation occurs (KUNZ et al. 1996 apud PECK et al., 2016, p. 40).

Roland (1970, p. 215), in his study to evaluate the influence of a progestogen (norgestrel in microdose) on cervical mucus, proceeded to endometrial aspiration to confirm the presence of sperm in the endometrium. The results of the tests on the cervix showed normal values, but no sperm was found in the aspirations, except for a user whose temperature curves and biopsies of the endometrium indicated a possible ovulation event, which warns of the aforementioned possibility of an ovulation event that alters the characteristics of the mucus as a result of serum hormonal changes.

Duijkers et al. (2015, p. 424) performed a comparative study between the progestogen drospirenone and desogestrel. Although the authors stated that the mucus permeability had been suppressed in both groups, what is certain is that in the case of drospirenone, the results of mucus quality in the first cycle were 15% of users, with a classification of the quality of the mucus as moderate and full, and in the second cycle 33%. In the case of desogestrel, in the first cycle the result was 34% and in the second 48%.

Kesseru et al. (1974 apud PECK et al., 2016, p. 40) demonstrated that, after a single dose of D-norgestrel, there was a change in the cervical mucus and a reduction in the amount of spermatozoa found in the cervix and in the uterine fluid. The analyses were performed only 3 to 10 hours after the contraceptive administration. More recent studies contradict this result (BRITO et al., 2005, p. 227; HERMANNY et al., 2012; DO NASCIMENTO et al., 2007 apud PECK et al., 2016, p. 40). Particularly in the study of Do Nascimento et al. (2007), viable sperm was found in the genital tract between 36-60h after intercourse and between 24-48h after LNG administration. The authors who found these results claim that the methodology currently used to identify the presence of spermatozoa is far superior to the methods used in previous studies.

Uterine endometrium alteration

On the uterine endometrium alterations, consider what has already been mentioned for the case of combined contraceptives, being that the changes caused by progestin only contraceptives are more profound than those caused by combined ones. POCs, having no estrogenic component in their composition, make the endometrium more vulnerable to instability (BASTIANELLI et al., 2020; VAN DEN BOSCH et al., 2002; GRAHAM, FRASER, 1982; AREF et al., 1973).

Fallopian Tubes

Regarding the effects of POCs on the fallopian tubes, we should take into account what was mentioned in the case of combined contraceptives. As mentioned before, progestins are associated with an increased risk of ectopic pregnancy. With the exception of Depo-Provera® users (BORGATTA et al., 2002), other POC users are at greater risk of having the embryo implanted in the Tube (MCCANN; POTTER. 1994, p. S21). With levonorgestrel implants (Norplant®), the risk was five times greater (FURLONG, 2002).

The rate of ectopic pregnancies in women who do not use contraceptive methods is 0.3%-3% while in mini-pill users is 2.8%-4.1% (GRAHAM, FRASER, p. 378, 1982; HARRISON-WOOLRYCH AND WOOLLEY, p. 5, 2003). This risk is greater with the use of levonorgestrel when compared to etonogestrel and injectable implants (CALLAHAN et al., 2015, p. 514).

Mechanism of Action of Progestogen-Releasing Intrauterine Systems

It is still not entirely clear how intrauterine devices or systems prevent pregnancy. Studies on women are limited, due to ethical issues, and the results are often inconclusive (ESHRE CAPRI, 2008, p. 199). Scientific investigations present the following possible modes of action of the IUD (STANFORD; MIKOLAJCZYK, 2002, p. 1702; MISHELL, 1998, p. 46S):

i) Pre-fertilization: interference in the ovulatory process; inhibition of sperm migration and its viability at the level of the cervix, endometrium and fallopian tubes; destruction or damage of the egg before fertilization; interference in the fertilization process;

ii) Post-fertilization: interference in the mobility process of the embryo formed along the fallopian tubes; interference in the proper development and survival of the embryo due to luteal phase deficiency; interference in the implantation process.

Effectiveness of ovulatory inhibition

The use of IUDs containing levonorgestrel (LNG-IUD) only inhibits ovulation partially, fifty percent in the first year of use and significantly less in the last years (BARBOSA et al., 1995 apud ESHRE CAPRI, 2008, p. 200). With this system, levonorgestrel is released directly into the uterine cavity and, therefore, systemic exposure to progestogen is low (APTER et al. 2014, p. 1657).

Barbosa et al. (1990, p. 51) published a value of 88% of ovulatory cycles after four years of use of IUD-LNG by nine regular menstruating women and 93% in fifteen users after seven years (BARBOSA et al., 1995, p. 85). Of these, only 47% in the first case and 58% in the second presented rupture and normal follicular growth.

Xiao et al. (1995, p. 359) reported a value of 78.5% of ovulatory cycles in fourteen users of IUD-LNG after 6 years. In the cases studied, only one presented insufficient luteal function. Nilsson et al. (1984, p. 53) published a result of 58% of LNG-IUD users, who revealed a normal ovulatory cycle, if the ovulation criterion would be a progesterone concentration greater than 5 ng/mL and 75% if the ovulation criterion corresponds to a progesterone concentration greater than 2 ng/mL. The authors conclude that the presence of the intrauterine system affected ovulatory function only slightly.

Sperm motility survival

The presence of the IUD, as a foreign body, causes an inflammatory reaction that produces a toxic environment for the sperm and compromises it on the way to the fallopian tubes (EL-HABASHI et al., 1998 apud MISHELL, 1998, p. 46S). The process of gland atrophy and decidualization observed in patients with LNG-IUD can also inhibit sperm survival (MISHELL, 1998, p. 46S).

The sperm moves from the cervix to the fallopian tubes and uterus within 1 hour. Investigations have shown that in the presence of IUDs and LNG-IUDs small amounts of sperm are recovered in the widest portion of the fallopian tubes (TREDWAY et al., 1975; KOCH, 1980 apud ESHRE CAPRI, 2008, p. 200). The quantities of LNG released by the IUD change the quality of the mucus, making it less suitable for sperm transport (KESSERU-KOOS; CAMACHO-ORTEGA, 1972; JONSSON et al., 1991 apud ESHRE CAPRI, 2008, p. 200).

According to Moraes et al. (2016), Natavio et al. (2013) and Apter et al. (2014) the quality of the cervical mucus obtained in users of LNG-IUD did not exceed the value of 10 (World Health Organization cervical mucus grading), which, according to the WHO, does not allow sperm to penetrate. The last two studies, however, cannot be claimed to justify changing in the quality of the mucus. Indeed, in the article published by Natavio et al. (2013), the mucus collections were made from the moment of IUD insertion. Its insertion occurred in mid cycle phase, on days that would naturally correspond to a low mucus quality value. After ovulation (about 3-4 days), the quality of the mucus naturally decreases, due to the production of progesterone by the body itself, so even in the absence of the LNG-IUD, the decrease in the mucus quality would be observed naturally. Hence it can't be concluded that the decrease in mucus quality is due to the presence of the device. Furthermore, according to Han, Taub and Jense (2017, p. 316), the fact that some users have ovulated during the research, prevents considerations on the effect of the presence of the device regardless of the natural hormonal level variations due to ovulation.

Apter et al. (2014) found that the majority of device users ovulated and profound progestogenic suppression of the endometrium was observed. The occurrence of ovula-

tion prevents one from concluding on the effect of the LNG-IUD independently of the hormonal variation caused by ovulation.

Barbosa et al. (1995), observed mucus of favorable quality in 69% of the analyzed ovulatory cycles. We must consider, also, the observation done by Lewis et al. (2010, p. 495), according to which, Barbosa et al., (1995) would not have followed the model defined by WHO, for cervical mucus tests, although this model was only published in 1999, after the experience. A previous study by Barbosa et al. (1990), published that in 55% of cycles, a good quality cervical mucus was observed (p. 57, 58), and the average obtained for the evaluation of penetration of the sperm was also good (p. 61).

Lewis et al. (2009, p. S27) published results of quality measurements of cervical mucus in the mid cycle phase, according to which 20% of 46 users of LNG-IUD had a good quality cervical mucus (score greater than ten). The percentage of good quality mucus in the controls was 71%. In 11% of the cases, the mucus was penetrable by sperm compared to 58% of penetrability among controls. Lewis et al. (2010), in an investigation involving fewer participants (14), observed 14% of cases with good quality cervical mucus, when compared with 69% in controls. Lewis did not observe penetration of mucus by sperm in experiments done in the middle of the cycle. However, it should be noted that a pregnancy occurred in one of the participants. The article does not describe the periodicity of the samples nor the moment of the collections, it just states that the analysis is relative to the mid cycle phase.

The published studies are not conclusive with regard to the extent to which progestogen-containing IUDs can reduce the likelihood of fertilization, by interfering with the sperm's migratory capacity to the fallopian tubes. Although there is a possibility for interference, evidence demonstrated cases of sperm presence in the fallopian tubes, concomitant with the use of progestogen containing devices.

Embryo quality and fertilization

According to Buskmiller et al. (2019, p. 1 and 5), there are studies that demonstrate embryo formation and also their loss in IUD users. The authors refer to the inconsistency of the studies carried out, claiming that the conclusions of some articles incorrectly diminish the evidence of post-fertilization mechanisms. In the case of IUD-LNG users, the studies that were performed, using β-hCG analysis, are small, but report 2.4% of cases of subclinical pregnancy loss.

Some studies have evaluated the occurrence of fertilization and the quality of embryo development, by removing eggs and embryos before implantation, from the fallopian tubes or uterus of women with and without LNG IUDs, in surgical sterilization processes (ORTIZ et al., 1996; ORTIZ; CROXATTO, 2007 apud ESHRE CAPRI, 2008, p. 199).

Alvarez et al. (1988) published a systematic study that is cited in different review articles. In this study, the authors sought to retrieve eggs from the fallopian tube washes of women with intrauterine systems without progestin deposits and in those containing progesterone and levonorgestrel, between 48 to 120 hours after the LH peak. In a first

experiment, 39% of IUD users had "eggs" in their fallopian tubes, compared to 56% of the control group. Alvarez et al proceeded to assess the degree of development of the supposed "eggs", post-coitus, in the fertile period of the reproductive cycle (-79 to + 11h relative to the LH peak). It was found that, through observation on optical microscope, 50% of the "eggs" found in the control group where embryos, whereas of the 5 "eggs" found in progestogen-IUD carriers, 4 did not show the appearance of fertilization and one presented an uncertain development stage, although its development was classified as abnormal, through microscopic inspections. The data did not include experience with a higher concentration LNG-IUD (e.g. Mirena® - 20 µg/mL). It should also be noted that the study was reduced to a single cycle of five IUD users, with no controlled time or certainty of insemination, with the exclusion of 4 patients with ambiguous results (SPINNATO, 1997). Buskmiller et al. (2019, p. 12-13) commented, regarding this study, that the authors assume that embryos should develop normally before entering the uterine cavity and enter it at a frequency comparable to that observed in non-IUD users. However, it is biologically possible that different factors could contribute to a post-fertilization embryo loss, as in the case of deficient luteal support, and may enter the uterine cavity late or at a reduced speed, with the possibility of post-fertilization effects occurrence. Even if embryos enter the uterine cavity at a normal rate, it does not mean that they are detected at a normal rate with the cross-sectional study they performed, as the timeline of embryonic loss is not known.

The authors also adopt a method of washing the fallopian tubes, which is used for the entire organ. However, only a single portion of the tube was removed and washed. To distinguish whether they would be in the presence of embryos or eggs, they assumed the fertilization time to be seventeen hours after the LH peak or the time of the last coitus, depending on which of the two was the last. If an embryo was found to be delayed in relation to the expected development for this period, it would not be classified as "normal", which in this study would correspond to 20% of the specimens found with LNG-IUD or progestasert.

The identification of specimens as an egg or embryo was made by visual inspection, which can be ambiguous. Ortiz and Croxatto (2007) reanalyzed the results of Alvarez et al. (1988) and, according to their visual analysis, one of the specimens identified with progestogen-IUD as uncertain would be an embryo, that is, 20% of cells recovered with the progestogen-IUD. This percentage is considerably high. In fact, fertilizations occur in users of progestogen-IUD, since embryos were recovered directly from the fallopian tubes. In addition, the rate of 0.2% (TRUSSEL 2011b apud TRUSSELL; GLOB, 2014) of unwanted pregnancies, proves that in fact embryos form.

We can deduce, comparing the values obtained experimentally for the embryos formed and the rate of unwanted pregnancy, that the progestogen-IUD acts at least partially by means of anti-implantation, or in other words, as abortive.

Uterine endometrium alteration

In LNG-IUD patients, the endometrium undergoes decidualization and atrophy of the glands, presenting itself abnormally thin, containing areas of fragile superficial vessels (LUUKKAINEN, 1994 apud MISHELL, 1998, p. 46S), compromising implantation and eventually survival and sperm capacitation, as mentioned above.

The inflammatory state caused by the presence of the LNG-IUD releases toxic products from white blood cells and endometrial cells, which hinder the implantation of the embryo (AGULLES SIMÓ, 2015, p. 94). Indeed, there are studies that show that the IUD also modifies cytokines and integrins in the endometrial lining, which may inhibit implantation if an embryo reaches the uterus (AMMALA et al. 1995, p. 773; SAVARIS, ZETLER, FERRARI, 2000, p. 1102).

According to Stanford and Mikolajczyk (2002, p. 1702), some authors indicate that the main biological effect of Mirena (20 µg/day) relies in endometrium suppression, which is likely to prevent implantation, although it can also result in inhibition of sperm migration.

Other authors claim that the system under study has no anti-implantation effect, but consider it essentially toxic to the survival of sperm, although without demonstrating it. The results are very varied. However, it was possible to identify the presence of sperm in the fallopian tubes of users of an intrauterine device containing levonogestrel, notwithstanding, in small quantities (TREDWAY et al., 1975; KOCH, 1980 apud ESHRE CAPRI, 2008, p. 200).

Fallopian Tubes

The progesterone present in the IUD causes a functional change in the fallopian tubes, in its epithelium and ciliary motility, which explains the high risk of ectopic implantation, when a pregnancy occurs (NELSON; MASSOUDI, 2016, p. 133; AGULLES SIMÓ, 2015, p. 95).

When pregnancy occurs in the presence of IUD, it is more likely to be ectopic, than in the case of women who do not use contraception, or those who become pregnant using oral contraceptives (SIVIN; TATUM, 1981; WHO, 1994 apud ESHRE CAPRI, 2008, p. 200). One of the explanations presented would be that IUDs are more effective in preventing pregnancy due to implantation in the uterus than when implantation occurs in the fallopian tubes, which would imply that in the presence of the device, some embryos reach the uterus, but are unable to implant. The extent to which the anti-implantation effect acts as a contraceptive mode of action is unknown because there are few published scientific data that describe it.

The percentage of ectopic pregnancies, clinically recognized, in IUD users, containing progesterone or levonorgestrel, is of 25% (STANFORD; MIKOLAJCZYK, 2002,

p. 1702). In an investigation carried out by Backman et al. (2004), the percentage of ectopic pregnancies among IUD-LNG users was 53% (BACKMAN, 2004, p. 50).

Controversy remains over the degree of contribution of pre- and post-fertilization mechanisms. Some publications claim that the main mechanism of action of LNG-IUD is to prevent fertilization via inhibition of ovulation and impaired sperm motility by altering the quality of cervical mucus. However, they also affirm that these systems directly or indirectly affect the endometrium, compromising the implantation of an eventually formed embryo, although they claim that no scientific evidence supports the hypothesis of an abortive effect (RIVERA et al., 1999, p. 1267).

Stanford and Mikolajczyk (2002, p. 1705) claimed that, even though the exact magnitude of the post-fertilization effects is not known, they are high, although it is certain that the predominant effect is to prevent fertilization. Even if fertilization occurs infrequently, the post-fertilization effect is very effective. When the contraceptive mechanism fails or is insufficient, the IUD prevents the embryo from implanting, with an efficiency of almost 100%.

Estimation of the Abortive Effect of Hormonal Contraceptives

As mentioned previously, the published contraceptive efficacy values correspond only to eggs that, once fertilized, implant successfully. They do not contemplate the fertilized eggs possibly eliminated by deficient luteal phase conditions, accompanied by inadequate morphology and functionality of the endometrium; or due to the arrival of the embryo in the uterus in a period that is outside the optimal time window.

In the following section, the word "abortion" will be used to describe an event that terminates an embryo that meets biological criteria for "life," so that a live birth does not result. This definition is based on the revitalize vocabulary used by ACOG and other national professional organizations.

It is possible to estimate the number of abortions for each class of contraceptives that we have evaluated, based on published data on the percentage of ovulation events that occurred despite the use of the contraceptive, and based on correction factors that include the probability of fertilization, the occurrence of pre-implantation, post-implantation miscarriage and the effect of cervical mucus.

Combined contraceptives

To estimate the abortive effect of combined oral contraceptives, formulas 1-4, indicated below, will be used. These were established according to Agulles Simó (2015, p. 84-86) reflections on the subject:

1) NA = EF – TUP
2) EF = PO x FEI x CM x (1 – APRI)
3) FEI = [100 – (PINF + PINFEC)]/100
4) TUP = UP x [1/(1-APOI)]

Legenda:

NA – Number of abortions/(woman x year);

EF – Corrected number of embryos formed with the use of the contraceptive/(woman x year);

PO – Percentage of ovulation events despite contraceptive use/(woman x year);

FEI – Percentage of fecundability of egg released (in decimal form);

CM – Cervical mucus effect;

APRI – Percentage of pre-implantation abortions, independent of contraceptive use (in decimal form);

PINF – Percentage of infertility;

PINFEC – Percentage of infecundability in ideal conditions of non-sterility nor physiological problem, maintaining several relationships in the most fertile phase of the woman's cycle (proximity to the LH peak);

TUP – Total number of unwanted pregnancies with contraceptive use, including post-implantation abortions/(woman x year);

UP – Percentage of unwanted pregnancies not including post-implantation abortions;

APOI – Percentage of post-implantation abortions (in decimal form).

Percentage of ovulation events that occur despite the use of contraceptives

Agulles Simó (2015, p. 84) proposed a value of 10% of ovulation events that occur even with the use of contraceptives. Although he does not mention where he gets this value, we assume that he has made an average of the different scientific values he presents throughout his article. In particular, on pages 83 and 84, he lists a set of published values that vary between 0.12% and 14%.

As mentioned before, Harrison et al. (2018), in the published review, refer that FLS are formed between 1.9% to 67.4% of cycles. Milsom and Korver (2012), published a percentage of ovulation (per individual) that varied between 0 and 30% of cycles, and in phasic regimes it varied between 0%-50%.

The calculation proposal consists of estimating the number of abortions based on the highest and lowest FLS values, determined by Harrison et al. (2018), added to the ovulation events and the LUF identified in each study, due to everything that was previously described about these structures. So the real value of ovulation events will be found somewhere in the interval, between the estimated limit values.

Based on table 2 presented by Harrison et al. (2018), the lowest value, which includes the number of identified ovulation events, the FLS and LUF, corresponds to 1.9% and the highest possible corresponds to 69%. However, according to the statistical data of unwanted pregnancies recorded (6%-8%), which will be referred to in a next step, it is not scientifically possible that the point estimate for the number of ovulation events that occurred with the typical use of combined oral contraceptives, be less than 4.2%. Those values of unwanted pregnancies necessarily imply the occurrence of a minimum number of escape ovulation events. Thus, we will use as a minimum value the one which in the table presented by Harrison et al. (2018) is the lowest but necessarily being

higher than 4.2%. Based on the table, the lowest value, which includes the number of ovulation events identified, the FLS and LUF corresponds to 5% and the highest possible corresponds to 69%.

Percentage of fecundability of egg released

Not all egg are likely to be fertilized, due to both the prevalence of infertility and the probability of fertilization for each fertile act of intercourse. To calculate this percentage, we must take into account the couple's percentage of infertility, in situations of occurrence of ovulation (PINF). According to Speroff, Glass and Kase (1994, p. 809 apud AGULLES SIMÓ 2015, p. 85), this value would be 13% and correspond to cases of defects in the female and male gametes.

According to Agarwal (2015, p. 1), global infertility affects about 15% of couples. Nachtigall (2006, p. 871) referred that, due to differences in definitions, methodology and differences between countries, the values vary between 4%–14%. Kamel (2010, p. 1) stated that infertility affects 13% to 15% of couples in the world, with a higher incidence in developed countries.

To consider these values, we must take into account the different factors that contribute to infertility. Some factors are more common in some countries than in others. Male factor infertility is responsible for 26-35% of cases; female factor infertility, 36-45%; mixed, 16-40%; and the remainder idiopathic or other (KARA; SIMONI, 2010; LINDSAY; VITRIKAS, 2015).

The values presented by Kara and Simoni (2010) will be adopted, since the value of 40%, presented by Lindsay and Vitrikas, attributed to combined causes (man/woman), is considered exaggerated, in comparison with other articles (e.g. Poppe and Velkeniers [2002]; Kanal and Sharma, [2006]; Krysiewicz1, [1992]). Of the causes mentioned, we only considered the idiopathic ones, since the cases of endometriosis and fallopian tube obstruction were eventually accounted for in the percentages of pre-implant abortion and ovulation problems are not considered in this case.

Thus, if we take the couple's infertility value of 14% and correct it, removing the explained female contribution (considering only the 10% idiopathic cause of the 36% female origin), this value becomes 9.5% (14-14 x 0.9 x 0.36). This will be our PINF (percentage of infertility) value.

As for the value of the percentage of infecundability (PINFEC), under ideal conditions of non-sterility nor physiological problem, and maintaining several relationships in the most fertile phase of the woman's cycle, Agulles Simó (2015, p. 85) proposed the value of 10%. Trussell (2012, p. 398) proposes a value of 15%, estimated from populations in which the use of contraceptives is rare or no longer use it in order to conceive. We opted for the value proposed by Agulles Simó (2015), as it corresponds to a more precise value in terms of ideal conditions and in terms of maintaining relationships in the most fertile phase of the cycle. Thus, for the calculation of the percentage of fecundability of egg released (FEI), using formula 3, we obtain the value of 0.805 ([100 - {9.5 + 10}] / 100).

Cervical mucus effect

Considering what was exposed on this theme in previous chapters, values were presented that include 75% of mucus of poor penetration quality (DI PIETRO; MINACORI, 1996), 95% (ROSSMANITH; STEFFENS; SCHRAMMT, 1997), 83 % and 89% (STEWARD et al., 2012).

We recall here what was said about the quality and diversity of the studies carried out, methodologies adopted, rapid change in the quality of mucus, caused by the variation in the concentration of progestogens or estrogens in circulation resulting from different factors, among them the failure to properly comply with the method of administration. Forgetting the pill, which almost half of women do (MARCUELLO, 1997, p. 668), may favor ovulation. The endometrium may not yet have recovered from its atrophic state and the cervical mucus barrier may have already been lifted by changes in the concentration of circulating hormones.

It is important to keep in mind that the poor quality of the cervical mucus is related to the process of ovulation inhibition. If ovulation is not inhibited, estrogen production will occur, which in turn changes the quality of the mucus, improving it, reminding also that a scarce or absent mucus may not necessarily prevent a pregnancy.

Thus, we chose to take the value presented by di Pietro and Minacori (1996) which coincides with the value of 75% proposed by Agulles Simó (2015, p. 85). With this value, the CM factor will be 0.25 (1-0.75).

Percentage of pre-implantation abortions

It is necessary to consider that there is a percentage of embryos that are spontaneously lost before implantation, regardless of the contraceptive action. According to Macklon, Geraedts and Fauser (2002), cytogenetic studies performed in vitro indicate that about 30% of embryos fail to implant, mainly due to chromosomal abnormalities in the gametes and embryo. These are data performed in vitro and do not mimic exactly what happens in vivo. In addition, it is not clear whether this figure will not include any factor relating to female sterility already accounted for before.

It should be considered the comment by Jarvis (2017, p. 15), who stated that the values proposed for total embryo loss are too exaggerated, and that are not confirmed by the available data. In the absence of adequate data to quantify the pre-implantation loss, many articles are limited to citing previously published values, as is the case of the article published by Macklon, Geraedts and Fauser (2002), cited more than 200 times.

The values presented by these authors correspond to an unedited representation of estimates published ten years earlier. The 30% figure for pre-implantation losses is considerably inaccurate. Some of its data is higher than that used to perform the analysis. Jarvis re-analyzed data from three studies (ZINAMAN et al., 1996; WANG et al., 2003; WILCOX et al., 1988) to conclude that, in normal healthy women, 10–40% is a plausible range for pre-implantation embryo loss. Agulles Simó (2015, p. 85) proposed a value of 20%. The mean value of Jarvis proposed range is 15%. It will be adopted for

calculation value, the same as that presented by Agulles Simó (2015, p. 85), 20%, which considerably represents an average of values proposed. Hence, APRI will correspond to 0.2.

Number of unwanted pregnancies

We present below some published values of the number of unwanted pregnancies during the first year of typical use and perfect use of combined contraceptives. According to Potter (1996, p. 13S), the pregnancy rate is 8% through typical use and 4% in perfect use.

According to Trussell (2011a, p. 398), based on data from the 1995 and 2002 of the National Survey of Family Growth, or from research and clinical investigations, the combined pregnancy rate of the combined oral contraceptive and progestin only is 9% for typical use and 0.3% for perfect use. The author mentions the possibility that some values might be underestimated, due to cover-up of induced abortions, or overestimated, by those who wish to attribute pregnancy to the ineffectiveness of the contraceptive.

The value proposed by Hatcher et al. (2003, p. 4-20) varies between 6% - 8% in the case of typical use and has a value of 0.1% in the case of perfect use. Wright and Johnson (2008, p. 907) quote Trussell (2004) to propose a value of 8% and 0.3%, respectively.

Winner (2012, p. 2004) presented a percentage of failure for combined oral contraceptives, together with those containing only progestogen, patches and rings of 4.8% in the first year. It is assumed that this value corresponds to the typical use, although in the article they do not refer to the quality of use.

Agulles Simó (2015, p. 85) proposed the value published by Hatcher (2008, p. 24), of 8% for typical use. Bradley et al. (2019, p. 11) analyzed the demographic and health surveys that took place between 1992 and 2014, having estimated the percentage of failure of oral contraceptives (combined and progestin only) as being 6.3%. Their estimates have not been corrected for cases of underreporting due to unmentioned abortions.

Based on the published data, we selected the value of 7% (average of the values presented) for the percentage of failure in the case of typical use and 0.3% in the case of perfect use. The average was not chosen in this case, as the value of 0.1% set by Hatcher (2003, p. 4-20) is considered too low. These percentages will correspond to the UP value in formula 4.

As stated by Agulles Simó (2015, p. 85), it is not clear whether these values correspond only to users who identified pregnancy after the first weeks of implantation, without considering the cases of post-implantation loss, so the correction of UP value will be made as indicated in the next section.

Percentage of post-implantation abortions

Zinaman et al. (1996, p. 503) recorded 13% of subclinical abortions identified only by hCG measurement (post-implantation). Macklon, Geraedts and Fauser (2002, p. 335) proposed a value of 30% for post-implantation spontaneous abortions. Wilcox

et al. (1988, p. 189) identified 22% of post-implantation abortions, in the study they published. Agulles Simó (2015, p. 85) proposed a value of 20%-25%. Based on these data, and in the opinion of Jarvis (2017, p. 15) mentioned above, we opted for the percentage of 20% (average of values is 21%), which corresponds to an APOI value of 0.2.

Estimation of the number of abortions

Estimates will be made for two possible ovulation rate values as previously described:

a) 5%; b) 69%.

For each of these rates the calculation will be made in the case of typical use and in the case of perfect use:

i) 7%; ii) 0.3%.

According to the observations presented above, we have the following values for the terms of formulas 1 to 4:

PO (a) = 5%; PO (b) = 69%; FEI = 0.805; CM = 0.25; UP (perfect use) = 0.3%; UP (typical use) = 7%; APRI = 0.2; APOI = 0.2.

Table 1 shows the different results obtained.

Table 1. Data referred to the estimate of the number of abortions caused by the use of combined oral contraceptives.

Percentage of ovulation	Typical use				Perfect use			
	EF	TUP	NA	1Y	EF	TUP	NA	1Y
PO (a) 5%	0.1046	0.0875	0.0172	58	0.1046	0.0038	0.101	10
PO (b) 69%	1.444	0.0875	1.357	< 1	1.444	0.0038	1.440	< 1

PO (percentage of ovulation despite contraceptive use); EF (corrected number of embryos formed - embryos/woman.year); TUP (total number of unwanted pregnancies - pregnancy/woman.year); NA (number of abortions - abortion/woman.year); 1Y (time, in years, necessary for an abortion to occur).

The results obtained indicate that the use of combined oral contraceptives can cause an abortion in less than a year if we use a 69% ovulation percentage as a starting point, both in the perfect (1.44) and typical (1.36) use. In the case of using an ovulation percentage of 5%, the probability of an abortion will be after 58 years in the case of typical use and after just less than 10 years with perfect use. Prolonged use of the pill without interruption is unusual. Between 33%-50% of the users abandon the contraceptive at the end of the first year (POTTER, 1991 apud AGULLES SIMÓ, 2015, p. 86), but for therapeutic purposes, therapies require a period that depends on the disease.

The result obtained for the perfect use mode is scientifically absurd when compared to the typical use mode. However, the explanation is given by the fact that the value of registered unwanted pregnancies is lower, which in the formula 1 causes the estimated number of abortions to be higher. The ideal would be to have access to the number of unwanted pregnancies correspondent specifically to each contraceptive compound, avoiding it to be too high for compounds with a lower percentage of ovulation events, in order to estimate a number of abortions closer to reality, for each contraceptive. It is

important to refer that, according to the formula used, the results vary a lot depending on the percentage of ovulation events considered. For example, if we consider 6% ovulation events, the number of estimated years for an abortion to occur with perfect use mode will be 26 and with typical use 8 years. With 8% ovulation events, the number of years decrease to 12 and 6, respectively.

Responding to objections

The result obtained for the 69% ovulation case gave a clearly higher probability than that proposed by Agulles Simó (2015), which corresponded to an abortion after about 11 years. This difference is due to the fact that the author used a single ovulation probability of 10%. The value is not so discrepant when we compare it with that obtained when using the ovulation percentage of 5%, in the perfect use mode, which corresponds to an abortion after less than ten years.

It should be noted that, probably, the value of 5% of ovulation occurrence is lower than the real percentage ovulation occurrence despite contraceptive use. We should bear in mind that the methods used to identify ovulation are not the most accurate, with the aggravation of using arbitrary Hoogland criteria, and in addition, multiple factors condition the ovulation process, as mentioned before. However, we wanted to include the value of 5% in the calculations, taking it as the lower limit of the range of the probability of ovulation occurrence.

Some authors arrive at results similar to those of Agulles Simó, using other formulas and assumptions, as is the case of considering that the percentage of fecundability per cycle corresponds to 25% of ovulation events under normal conditions and corrected according to age. However, as pointed out by Agulles Simó (2015, p. 86), it is methodologically more correct to use the percentage of fecundability as previously calculated, as the period of interest is the one in which ovulation actually occurs.

Other authors used a percentage of fecundability in the fertile window (10 days) of 30% (a very low value), which would correspond to the daily and not accumulated probability. They do not consider spontaneous pre- and post-implantation losses (subclinical abortions) either. Some authors also use the Pearl index to estimate the number of abortions caused by the contraceptive. The Pearl index corresponds to the number of pregnancies per 100 women who took the pill during 12 cycles. However, the value is obtained by dividing the number of pregnancies by the number of years of use, but the probability of becoming pregnant decreases with years of use. In addition, participants who are more likely to become pregnant often become pregnant in the first year and withdraw from the study project, which contributes to the decrease in the Pearl index (AGULLES SIMÓ, 2015, p. 86).

For example di Pietro and Minacori (1996, p. 879-880), estimated one abortion every ten years using a Pearl index of 0.07%-0.5% (lower than the values of unwanted pregnancies through typical use), and consider a fecundability of 25% of ovulation per cycle (lower than this study's - 80.5). The authors do not mention the corrections regarding spontaneous abortions before and after implantation, nor regarding the cervical

mucus effect. As another example, Marcuello, (1997, p. 668) quoted Kippley (1989) who proposes the probability of an abortion every 88 menstrual cycles (6.7 years). No reference is made to how the calculation was made.

However, the use of combined oral contraceptives for more than 2 years increases the likelihood of abortions that may be associated with changes in the endometrium caused by the use of these compounds (GARCÍA-ENGUÍDANOS, 2005, p. 1866).

According to information given previously, we can affirm that the estimate of abortions obtained in the case of combined oral contraceptives is extended to patches and vaginal rings.

Progestion only contraceptives

To calculate the estimate of the abortion effect of progestin only contraceptives, we will proceed in the same way as described for combined contraceptives. We will distinguish, however, between the pills, implants and injectables, as they have a different contraceptive effectiveness, unlike the different routes of administration among combined contraceptives.

Oral contraceptives (minipill)

Percentage of ovulation events that occur despite contraceptive use. Progestin only contraceptives are less effective in inhibiting ovulation, as they do not have the estrogen reinforcement in their composition, with the aggravating factor that progestogen concentrations are sometimes lower than those found in combined contraceptives. Partial inhibition of ovulation can also be accompanied by a luteal phase deficiency that compromises the embryo's implantation and survival.

Based on what we described earlier, the percentage of ovulation events that occur during the use of progestin-only contraceptives, published by the different authors, vary between 50% of total suppression and 30%-40% of inconstant suppression with deficiency of luteal phase, 28.6%-39.5% (norethisterone), 28.6%-65.5% (levonorgestrel), 0%-3.4% (desogestrel). In the review published by Harrison et al. (2018), in the two studies reviewed, 17.4% and 37.5% of FLS were found without ovulation nor LUF, in the case of dienogest, and 1.9% of ovulation with drospirenone, but 42.6% of FLS and 1.7% of ovulation with desogestrel and 60.3% of FLS. We see that in terms of observed ovulation (according to Hoogland's arbitrary criteria), in the case of desogestrel, drospirenone and dienogest they were few, but the percentage of FLS was high.

The published rate of breakthrough ovulation with these compounds are quite high when compared to most of the published values for combined contraceptives. In order to calculate the percentage of abortions caused by progestin-only compounds, we can adopt the value of 50% of ovulation occurrence (our PO in formula 2), as suggested by Agulles Simó (2015, p. 92), since it is a value which translates, on average, most of the results observed, especially those that include ovulatory states of the FLS type.

Cervical mucus effect. As mentioned before, publications that evaluated the influence of oral progestogen on cervical mucus report decreases in mucus quality in 52% to 85% of the users. Some results mention only a reduction in quality, without referring the percentage, and others present normal values for the presence of sperm in the cervix, but absence in the uterus. However, it is known that sperm tends to direct itself to the ovary where ovulation occurred. The value that will be adopted for calculation purposes will be 75% (the average of the values is 74%), so the CM value will be 0.25.

Number of unwanted pregnancies. As explained in determining the number of unwanted pregnancies with combined contraceptives, the publications have presented common values for these and progestin only contraceptives, whence the same percentages of 7% (typical use) and 0.3% (perfect use) will be adopted.

Estimation of the number of abortions. The values of the percentage of fecundability, pre-implantation and post-implantation abortions are the same used in the calculations described for combined contraceptives. The parameters to be entered in formulas 1 to 4 will be:

PO = 50%; FEI = 0.805; CM = 0.25; APRI = 0.2; APOI = 0.2; UP (perfect use) = 0.3%; UP (typical use) = 7%.

Table 2 shows the results obtained for typical and perfect use cases.

Table 2. Data referred to the estimate of the number of abortions caused by the use of progestin only contraceptives.

Percentage of ovulation	Typical use				Perfect use			
	EF	TUP	NA	1Y	EF	TGI	NA	1Y
PO 50%	1.0465	0.0875	0.959	1.04	1.0465	0.0038	1.043	< 1

PO (percentage of ovulation despite contraceptive use); EF (corrected number of embryos formed - embryos/woman.year); TUP (total number of unwanted pregnancies - pregnancy/woman.year); NA (number of abortions - abortion/woman.year); 1Y (time, in years, necessary for an abortion to occur).

The results obtained indicate that the use of progestin only oral contraceptives might cause an abortion in less than a year, in the case of perfect use, and in just over a year, in the case of typical use. As we mentioned for combined contraceptives, the result obtained for the perfect mode of use is similarly high when compared to the typical use mode but very similar to the one of Agulles Simó (2015, p. 92), which corresponds to an abortion in little less than a year.

The rates of the continuity of use of these compounds, after the first year, are around 60% (WERE, 1997 apud GRIMES et al., 2010) and 75% (BRIGGS et al., 2016), although within the scope of the study of this work the extension of its use is subject to the treatment period, as mentioned for the case of combined contraceptives.

Implants

Percentage of ovulation events that occur despite contraceptive use. Based on what was already exposed, the ovulation values in the presence of the implant can vary between 1% and 75%. Values tend to increase over time. Harrison et al. (2018) did not include data of progestin-only implant so we do not know how many FSL or LUF can be formed and eventually contribute to ovulation events. Taking this into account the value of 40% will be used to calculate the abortions estimate although the average of published values is 31%.

Number of unwanted pregnancies. The percentage of unwanted pregnancies during the use of implants is lower than that of POPs. According to Trussell (2011a, p. 398), based on data from the National Survey of Family Growth of 1995 and 2002, or clinical research and investigations, the percentage of unwanted pregnancies with progestin only implants (Implanon) is 0.05%, both in typical and perfect use. The same value is presented by Agulles Simó (HATCHER, 2008, p. 93 apud AGULLES SIMÓ, 2015, p. 93) and Trussel (2011b apud TRUSSELL; GLOB, 2014).

Yet the values presented by Hatcher et al. (2003, p. 4-20) are 0.1% for typical and perfect use. Based on the published values, we selected 0.05% for the percentage of failure in typical and perfect use cases, because it corresponds to more recent data and consider also that the average of values is not significantly different from this (0.07).

Cervical mucus effect. Publications that evaluated the influence of progestogen implants, on cervical mucus, refer to decreases in mucus quality that include a range value of 31%-93%. The value that will be adopted for calculation purposes will be 75% (the average of the values is 73%). You then have a CM of 0.25.

Estimation of the number of abortions. The percentage of fecundability, pre- and post-implantation abortions are the ones used in the estimate for combined contraceptives. The parameters to be entered in formulas 1 to 4 will be:

PO = 40%; FEI = 0.805; CM = 0.25; APRI = 0.2; APOI = 0.2; UP (perfect / typical use) = 0.05%

Table 3 shows the results obtained.

Table 3. Data referred to the estimate of the number of abortions caused by the use of the progestin only implants.

Percentage of ovulation	Typical and perfect use			
	EF	**TUP**	**NA**	**1Y**
PO 50%	0.8372	0.0006	0.8366	1.2

PO (percentage of ovulation despite contraceptive use); EF (corrected number of embryos formed - embryos/woman.year); TUP (total number of unwanted pregnancies - pregnancy/woman.year); NA (number of abortions - abortion/woman.year); 1Y (time, in years, necessary for an abortion to occur).

The results obtained indicate that the use of progestin only implants can cause an abortion in just over a year (1.2 years). This result was very similar to the one obtained by Agulles Simó (2015, p. 92), with 0.96 abortions per year, although he used 50% for the ovulation occurrence.

Injectables

Percentage of ovulation events that occur despite the use of contraceptives. Agulles Simó (2015, p. 93) considered that in the case of injectables, the rate of breakthrough ovulation is practically null and, if it occurs, it does not end in abortion. The published data, although limited, did not allow us to infer such a conclusion. In fact, the bibliography claims that the inhibitory effect is high, and the barrier effect of the cervical mucus is observed, but also the atrophy of the endometrium, with the aggravating fact that in some publications the occurrence of ovulation or ovarian activity was determined indirectly, based on progesterone concentrations, as in the case of Ortiz et al. (1977).

Petta et al. (1998a), used ultrasound measurement, to observe ovulation in about 30% of participants in whom the injection was given between days 8-13 of the menstrual cycle. No ovulation was observed in cases where the injection was administered between days 8 and 9, but attention must be paid to the criteria used to identify ovulation events. Unfortunately, the review by Harrison et al. (2018) did not include studies of injectables, for which we have no information on the percentage of formation of LUF and FLS. There are, however, data on the occurrence of undesirable pregnancies with these compounds, so in fact, ovulation events are not completely inhibited with those injectables.

Although we do not have sufficient data regarding breakthrough ovulation during progestin-only injectables use, we can consider the estimation for a particular situation that would correspond to the administration of the injection in a period that would not be the most appropriate, which can occur in certain situations or in less developed countries. This value also includes the possibility of the decrease in the concentration of the contraceptive over time. This situation can be described by the 30% of breakthrough ovulation published by Petta et al. (1998a).

Number of unwanted pregnancies. Borgatta et al. (2002, p. 170) published a value of 0.43 for unwanted pregnancies per 1000 women a year. The authors stated that this is a value that is underestimated and that in reality it must be higher. The value of unwanted pregnancies proposed by Hatcher et al. (2003, p. 4-20) for the use of Depo-Provera® and injectable norethisterone enanthate in the typical and perfect use is 0.3%.

According to Trussel (2011a) and Trussel (2011b apud TRUSSEL; GLOB, 2014), the value of unwanted pregnancy that occur with the use of these compounds is 6% for the typical mode of use and 0.2% for the case of perfect use.

Based on the published data, the value of 6% was selected for the percentage of failure, corresponding to the typical mode of use, since the experimental data consid-

ered will refer to a situation of not perfect use, and a period in which the concentration of the progestogen in the blood could be decaying. This value corresponds to the UP value indicated in formula 1.

Cervical mucus effect. Petta, Faundes and Dunson (1998b) reported the effects of administering Depo-Provera®: after 24 hours of administration, the quality of the cervical mucus was identified as being poor in about 90 % of users. Measured the sperm penetration capacity in vitro, this corresponded to a value of less than 1 cm, in 87% of users. Three days after the injection, with the exception of one user, all had poor mucus quality (97%).

In view of the aforementioned information, a value of 90% of altered cervical mucus quality was selected for the purpose of calculating the number of abortions, which corresponds to a cervical mucus effect (CM) of 0.1.

Estimation of the number of abortions. The values of the percentage of fecundability, pre- and post-implantation abortions are the same used in the previous estimates. The parameters to be entered in formulas 1 to 4 will be:

PO = 30%; FEI = 0.805; MCE = 0.1; APRI = 0.2; APOI = 0.2; UP (typical use) = 6%.

Table 4 shows the results obtained.

Table 4. Data referred to the estimation of the number of abortions caused by the use of progestin-only injectables.

Percentage of ovulation	Typical use			
	EF	**TUP**	**NA**	**1Y**
PO 30%	0.2512	0.075	0.1762	5.7

PO (percentage of ovulation despite contraceptive use); EF (corrected number of embryos formed - embryos/woman.year); TUP (total number of unwanted pregnancies - pregnancy/woman.year); NA (number of abortions - abortion/woman.year); 1Y (time, in years, necessary for an abortion to occur).

The results obtained indicate that the use of progestin-only injectables can cause an abortion in less than six years with the typical use mode, for the specific situation described. The rates of continuity of use after one year in the case of Depo-Provera® are 56% (TRUSSEL, 2011a, p. 398; TRUSSEL, 2011b, apud TRUSSEL; GLOB, 2014, p. 4).

IUD containing LNG or Progestogen

Agulles Simó (2015) did not calculate the estimate of abortions caused by the use of progestogen-IUD, he just proposed the value presented by Stanford and Mikolajczyk (2002), which corresponds to 0.8-1.2 abortions per year. Adopting the same line of reasoning used until now, the data that will permit to calculate the estimate of abortions caused by these contraceptives are presented below.

Percentage of ovulation events that occur despite the use of the contraceptive

From the data presented, the ovulation values published in the literature vary between 50% and 93%, since it increases with the years of use. For calculation purposes, considering the first year of use, the value of 50% has been chosen.

Cervical mucus effect

Some investigations referenced previously demonstrated that in the presence of LNG- IUDs, small amounts of sperm are recovered in the ampullatory portion of the fallopian tubes. The values published and presented allow adopting the value of 75% for the cervical mucus effect; so, CM will be 0.25.

Number of unwanted pregnancies

According to Trussel (2011a) and Trussel (2011b apud TRUSSEL; GLOB, 2014), the rate of unwanted pregnancies per 100 women during the first year of Mirena® use is 0.2, both in the case of typical and perfect mode. But according to Sivin et al., (1990 p. 361) at five years of use the value rises to 0.6-1.6, and about 80% of women continue to use it after the first year (HATCHER et al. apud AGULLES SIMÓ, 2015, p. 97). For calculation regarding the first year of use, the value of 0.2 was taken.

Estimation of the number of abortions

Using the percentage of fecundability and of pre- and post-implantation abortions used in the previous estimates, the parameters to be introduced in formulas 1 to 4 will be:

PO = 50%; FEI = 0.805; CM = 0.25; APRI = 0.2; APOI = 0.2; UP (typical / perfect use) = 0.2%.

Table 5 shows the results obtained.

Table 5. Data referred to the estimated number of abortions caused by the use of an progestogen-IUD.

Percentage of ovulation	Typical/perfect use			
	EF	**TUP**	**NA**	**1Y**
PO 50%	1.0465	0.0025	1.044	1.0

PO (percentage of ovulation despite contraceptive use); EF (corrected number of embryos formed - embryos/woman.year); TUP (total number of unwanted pregnancies - pregnancy/woman.year); NA (number of abortions - abortion/woman.year); 1Y (time, in years, necessary for an abortion to occur).

The results obtained indicate that the use of these compounds can cause an abortion after one year. The result is similar to that presented by Stanford and Mikolajczyk (2002), which corresponded to 0.8-1.2. If, instead of using a percentage of post-implantation abortion of 20, we use the 2.4 value published by Buskmiller et al. (2019, p. 5), the number of abortions will be practically the same. It depends mainly on the number of embryo formed.

Discussion

In table number six, we systematically present the number of years estimated for the probability of an abortion occurrence, for each of the main classes of hormonal contraceptives studied, and in the conditions previously described.

Table 6. Time in years for an abortion to occur.

Contraceptive	Typical use	Perfect use
COC (5% Ovulation)	58	10
COC (69% Ovulation)	< 1	< 1
POC oral	1.0	< 1
POC Implant	1.2	1.2
POC Injectable[§]	5.7	-
IUD with progestogen	1.0	1.0

[§] This value corresponds to the specific situation described for the calculation.

The estimates obtained do not result from direct biological measurements, but from indirect evidence of considerable quality, which are expressed as a probability. Other authors obtained similar results, except that they did not use a probable ovulation rate of 69%, in the case of COCs, since they did not consider the arbitrariness of the Hoogland classification method, well warned by Harrison et al. (2018). These estimates were obtained from data that involved several individuals, several methodologies and regarded different compounds. It follows that it cannot be said with certainty that the woman who uses them for therapeutic purposes will cause an abortion after less than a year (using the 69% ovulation rate, for COCs) or after 10 years (ovulation rate 5% and perfect use for COCs) or 58 years (ovulation rate 5% and typical use for COCs). However, it cannot either be said, with certainty, that the COC use will not provoke the abortion.

The value of 58 years surpasses the number of years of woman's fertility, and, therefore, would correspond in practice to a zero probability of the occurrence of abortion. Nevertheless, abortion can be anticipated and occur in the first treatment cycle or never occur (AGULLES SIMÓ, 2015, p. 87). The result found with an ovulation rate of 5% corresponds to a very low probability (10 or 58 years).

Probably the most correct would be, in the case of the ovulation percentage of 5%, just to perform the calculations with the value of unwanted pregnancy proposed for perfect use, since it is a very low percentage of ovulation events that probably occurs only when COC´s use mode is perfect. Besides that, the ideal would be to have access to the number of unwanted pregnancies correspondent specifically to each contraceptive compound, avoiding it to be too high for compounds with a lower percentage of ovulation events, in order to estimate a number of abortions closer to reality, for each contraceptive. Note that if we consider an ovulation rate of 8% instead of 5%, the probability of an abortion occurrence decreases to 6 and 12 years, depending on the use mode.

In the case of progestogen-only contraceptives, there is experimental evidence that their anovulatory effect is much less efficient than that of combined contraceptives, which in statistical terms resulted in a probability of abortion occurrence in less than a year of use (as shown in table six), or just over a year (in the case of implants). In the case, of these contraceptives we have the aggravating factor of the increased probability of ectopic pregnancy occurrence, with the exception of Depo-Provera®, which might put the patient's own life at risk. In the case of injectables, the probability of abortion was lower (one abortion in almost six years of use), and this calculation was specifically for the case of injection application in inadequate days of the cycle.

In the case of intrauterine devices containing levonorgestrel or progestogen, the estimates obtained predict, the probability of an abortion occurrence after one year of use. In this case, as in the progestogen-only contraceptives, the aggravating factor is that its use is associated with a higher occurrence of ectopic pregnancy.

Conclusion

Current hormonal contraceptive compositions available on the market do not completely inhibit ovulation. This fact, although more pronounced in the case of POCs, can be observed in all classes of hormonal contraceptives and may increase because of multiple conditions. These ovulation events can generate embryos. Research confirms considerable functional and morphological alteration of the endometrium, caused by the use of the contraceptive, making it unfit for the implantation, which may cause embryo loss. A change in the motility of the fallopian tubes may also delay or advance the arrival of a possible embryo in the uterus, so that it may not be suitable for implantation.

The collected scientific data enables the determination of the probability of the undesired consequence that may accompany the use of hormonal contraceptives, that is, embryo loss, via post-fertilization effect.

Although the estimates of the probability of abortion occurrence, due to the use of hormonal contraceptives, were based on biological values that do not result from direct measurements (once that currently there are no methods that allow it to be done), the calculations were based on scientific data of considerable value, which ensure the validity of the representativeness of the results obtained, in the probabilistic scope.

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ANNEXES

ANNEX A. Table of Hoogland criteria for Ovarian activity.

Hoogland terminology	Hoogland criteria
No activity	a) Dominant follicle < 10 mm diameter
Potential activity	a) Dominant follicle 10-13 mm diameter
Nonactive FLS	a) Dominant follicle > 13 mm diameter
	b) Follicles may rupture or not
	c) Serum estradiol concentration > 0.1 nmol/L in follicular phase
	d) Serum progesterone concentration any
Active FLS[¥]	a) Dominant follicle > 13 mm diameter
	b) Follicles may rupture or not
	c) Serum estradiol concentration > 0.1 nmol/L in follicular phase
	d) Serum progesterone concentration > 5 nmol/L
LUF[§]	a) Dominant follicle > 13 mm diameter
	b) Decrease in follicle size by less than 50% or occurring not within two to four days or not occurring at all. This is identified as "no follicular rupture" even if follicular rupture occurred but de decrease in size detected was inferior to 50%
	c) Serum estradiol concentration > 0.1 nmol in follicular phase
	d) Serum progesterone concentration > 5 nmol/L in luteal phase
"Ovulation"	a) Dominant follicle > 13 mm diameter
	b) Decrease in follicle size by 50% or more occurring within two to four days or not occurring at all. This is identified as "follicular rupture"
	c) Serum estradiol concentration > 0.1 nmol in follicular phase
	d) Serum progesterone concentration > 5 nmol/L in luteal phase

[¥] Follicle like structure;
[§] Luteinized unruptured follicle.