Oral Contraceptives and Cancer Risk: Analyzing the New Evidence.

Jorge Sánchez Lander*

Paula Cortiñas Sardi**

"It is usually unknown what is closest"

Rosanna Di Turi, El Libro del Ron, Caracas 2015

Oral contraceptives (OCs) have become the most prescribed medication in the US in women between 18-44 years of age[1]. A pharmacological measure with a favorable impact on the reduction of maternal and child mortality at the global level, particularly in the developing countries. From a social point of view, OCs have been a determining factor in achieving greater freedom, development and equity for women, which translates into an undeniable benefit to society in general.

The contraceptive benefits, by allowing the empowerment of women thanks to the ability to plan their offspring based on their desires and living conditions, are indisputable. Non-contraceptive contributions, such as the reduction of risk in neoplastic pathologies as endometrial and ovarian cancer, are increasingly notable. However, like any medication used in healthy patients, it has much more stringent tolerance and safety requirements than that medication aimed to solve a disease or interrupting a risk factor, such as hypertension or diabetes mellitus. Tolerance to side effects or increased risk for any pathology are perceived and accepted, for example, in an antihypertensive that with a vaccine or a CO. So it is a fact that any pharmacological intervention, in healthy women,

will be scrutinized by a magnifying glass of greater amplification. A greater demand has been generated in the way in which the risk is evaluated statistically, thanks to a greater effort to obtain a more robust evidence and a reliably measure of the possible relation with the new formulations of OCs. It has become a necessity to respond adequately to a society with greater access to information of all kinds and with a deep interest in knowing the risk profile of each measure that is assumed

It is possible to affirm that since the last three decades, there has been a favorable trend of perception characterized by a healthier profile, through proper nutrition, systematic exercise and the prevention of the two main enemies of the world population such as cancer and cardiovascular diseases. However, this interesting phenomenon can be tempered by an extreme cancerophobia that moves capriciously in a spectrum of public opinion fueled by excessive media pressure for or against the use of OCs. There is where the doctor has the challenge of becoming an element of balance that responds reliably, based on the available evidence, the questions that each woman has when considering to start using OCs.

Evidence gathered to date in terms of the relationship in the risk of breast or gynecologic cancer can be divided into those published before 2012 and those published after that date. The publication of results from large cohort studies, such as the Oxford Family Planning Association (Oxford-FPA) in 2013[2], the Royal College of General Practitioners' Oral Contraception Study[3] (RCGPS) in 2017 and the meta-analysis of Gierisch JM et al of Duke University in North Carolina[4] (MDU), published in 2013, has generated an interesting turning point. The new evidence is presented more carefully, as regards the methodology for the inclusion and analysis of the data. Likewise, in these three studies, there is a clear interest in aiming to evaluate the risk with the new formulations and progressively interrupting an existing data that preponderantly used formulations, in terms of the dose of ethininyl estradiol (EE), ostensibly much higher than the current formulations. Specifically in the Gierish meta-analysis, one of the inclusion criteria was to evaluate studies published since the year 2000, in order to achieve a date as close to the current formulations. In the Oxford-FPA recruitment was conducted between 1968 and 1974, most women (67%) used OCs combined with 50 mcg of EE, 18% of them with less than 50 mcg of EE, 2% with doses greater than 50 mcg and 13% used only progestins. In view of this change, it will necessarily be changes observed in the next years in the statistical trends of risk that will be a better reflection of the use of the current formulations.

OCs and breast cancer risk:

The general perception that exists about the possible relationship between the increased risk of breast cancer among OCs users remains a strong pattern of thinking in society. However, there has been a change in statistical trend patterns, based on the new available evidence. In the MDU, which included 76 studies, with more than 100 subjects per study,

there was a discreet increase in risk for all studies (OR 1.08, 95% CI 1.03-1.17) and for all studies performed in the USA (OR: 1.03 (CI, 0.93-1.14), the latter without achieving a statistically significant difference. There was no relationship between risk and time of use (1 month - 120 months), with a very important heterogenicity in the sample. A risk increase of 0.89% was proportionally estimated, a figure which is obviously lower than that obtained for attributable risk in the RCGPS, which stood at 3%.

The analysis of the data of the Oxford-FPA did not show an increase in the risk of breast cancer in users of OCs independently of the duration of the medication, including above the 8 years. Resulting in an RR of 1.0 (0.9-1.1) for the consolidated analysis of all durations.

Regarding the analysis of risk in users, related to the time elapsed since the last dose, there was no increase in Relative risk (RR), ranging from a RR of 1.1 (0.9-1.4) with less than two years and 0.9 (0.8 -1.2) for those with more than 28 years since the last dose. In the RCGPS there was a statistically valid increase in the incidence rate in current and recent users, less than 5 years after the last dose (RR 1.48, CI 1.10-1.47), which was progressively corrected to reach an RR of 0.75 (CI, 0.60-0.93) above 35 years from the suspension.

Cervical Cancer and OCs:

Although recent evidence points to an increased risk of cervical cancer among OCs users, available studies have failed to consistently establish among users with persistent human papillomavirus (HPV) infection. The model of carcinogenesis based on HPV infection is perhaps the most robust model to explain the events that lead to malignant transformation at the level in the transformation zone cells. Although the action of estrogens as cofactors promoting virus-initiated carcinogenesis has been proposed as a mechanism to explain this possible relationship still does not fit satisfactorily with a convincing explanation. However both the Oxford-FPA and the RCGPS have reported an increased risk among OCs users.

For the Oxford-FPA this increase is dependent on the time of exposure, with a progressive raise from two years (RR 2.3, CI 0.8-7.1) and that, for all durations, reaches a RR of 3.4 (CI: 1.6-8.9). This increase showed a trend among users for more than six years, with a peak of 2 years after the last dose (RR: 5.3, CI 2.2-15), and decreasing very gradually at 12 years or more of the last dose (RR: 3.2, CI 1.0-10.2).

For RCGPS, the attributable risk was 25.2%, a risk considerably higher than other studies. As for the time since the last dose, there was a trend different and very robust from Oxford-FPA with an increase in the incidence rate, statistically significant, in current users and a recent (less than 5 years) of 2.34 (1.24-4.34) and that is corrected progressively, to reach an incidence rate of 0.51 (CI 0.16-1.67) beyond 35 years after the last use.

In the MDU, an increased risk for cervical cancer was shown with an OR of 1.29 (CI 0.88-1.91) and for carcinoma in situ with a OR:2.54 (CI, 0.95- 6.78), which were not statistically

significant. Regarding the relation with the time of use in women with HPV infection, a significant increase was reported among users between 5 and 9 years (OR: 2.82, CI, 1.46-5.42) and for users with 10 or more years (OR: 4.03, CI, 2.09-8.02). In women without HPV infection, an increased risk was reported that did not reach a statistically significant difference (OR: 1.21 (CI, 0.91-1.61) and was not related to the time of use.

In a study published in 2016 by the European Prospective Investigation into Cancer and Nutrition5, performed in 308,036 patients for 9 years, the use of OCs for more than 15 years was associated with an increased risk for NIC3 / CIS (HR: 1.6) and cervical cancer (HR: 1.8). However, this work group considered that adherence to primary prevention and screening schemes, through prophylactic vaccination against HPV, would allow an efficient counterbalance of this risk and prevent a significant group of women from obtaining the important contraceptive and not contraceptives benefits, especially in the reduction of other neoplasias such as endometrium, colon and ovary.

Ovarian, endometrial and colon cancer in relation to OCs use:

One of the major non-contraceptive benefits of OCs is the protective effect, through decreased risk, against ovarian cancer, the most lethal gynecological neoplasia, and without an efficient screening model. It is estimated that for more than 50 years nearly 200,000 new cases and 100,000 deaths have been avoided thanks to OCs use[6]. Today, it is considered that the use of OCs is the most effective measure in reducing the risk of ovarian cancer, after the risk intervention annexectomy, only reserved in patients with high genetic risk.

In the Oxford-FPA results a progressive and persistent over time, robust decrease risk for ovarian cancer and endometrium is evident. In relation to the time of use, a RR of 0.5 (IC: 0.3-0.7) was recorded for endometrial cancer and 0.5 (IC; 0.4-0.7) for ovarian cancer, for all durations. This effect was observed after two years of use and remained significantly up to 20 years after the last endometrial cancer (RR 0.4, IC 0.2-0.7) and up to 28 years for ovarian cancer (0.6, CI 0.3-0.9). These data coincide significantly with the RCGPS in its 2017 report, which showed that the use of OCs was associated with a 34.3% reduction in expected cases of endometrial cancer and 33.6% in ovarian cancer. Similarly for the MDU, a protective effect was recorded for endometrial cancer with an OR of 0.57 (CI, 0.43-0.77) for all included studies and an OR of 0.34 (CI, 0 .25-0.47), for studies conducted in the USA.

In terms of endometrial and colon cancer, two of the neoplasias with the highest incidence in women, the reduction of risk is considered one of the benefits with greater epidemiological extent. For colon cancer, the reported risk reduction in MDU for all studies was statistically significant (OR: 0.86 CI, 0.79-0.95). This decrease in risk did not reach a significant difference in the US studies by a discrete difference in the confidence interval (OR: 0.83 CI, 0.69-1.01). For RCGPS, the percentage decrease in expected cases among OCs users was 19.1%.

In relation to other neoplasms, RCGPS reported a marked reduction in the risk of any neoplastic pathology of 4.2%, of 26.4% for lymphohematopoietic neoplasms, 12.5% for esophagus-stomach and 18.7% for hepatic and vesicular cancer. On the contrary, there was an increase in the risk attributable to skin cancer, excluding melanoma of 9% and of 7.2% only for malignant melanoma. For thyroid cancer there was an attributable risk increase of 5.8%. Particular mention was made of lung cancer, whose attributable risk was raised among users by 16.8%, a cause for concern in a high-incidence pathology and a trend with an alarming global rise. However, when the risk of lung cancer was differentiated among OCs users between non-smokers and smokers, an IRR (Incidnece Rate Ratio) of 0.73 (0.42 -1.26) and 1.34 (1.06 - 1.69), respectively. This allows to interpret that the increased risk attributable to lung cancer is more related to smoking than to ACO use.

Risk is an inherent fact of life itself. The quantification of risk, through the increasingly structured statistical tools and registration, is a very representative element, but it is static and must be contrasted with other aspects. An intelligent view of risk involves considering the possible benefits or prejudices of assuming a medication with a given risk profile. The question that we must ask before a woman who request our opinion on whether to start an oral contraceptive plan is whether the contraceptive and non-contraceptive benefits clearly outweigh the possible risks. In this way the decision-making will finally be in the hands of a woman oriented by her doctor. While the trend of evidence regarding the use of OCs has shifted towards a more secure and balanced view, the perception pattern still remains anchored in considering OCs as the usual suspects. Indicating an OCs based on the most recent evidence and the clinical characteristics of women is what must prevail. Denying the opportunity for contraceptive and non-contraceptive benefits based on close myopic vision will be as inconvenient as dismissing potential risks.

*Cirujano oncólogo , especialista en ginecología oncológica y mastología. Servicio de Ginecología Oncológica Instituto de Oncología Luis Razetti y Clínica Santa Sofía, Caracas, Venezuela.
** Especialista en Ginecología. MSc en Reproducción Humana. Coordinadora del Programa de Prevención de Cáncer de Cuello Uterino Salud Chacao. Instituto de Oncología Luis Razetti y Clínica Santa Sofía, caracas, Venezuela.

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