GYNECOLOGY

Association between ovarian stimulators with or without intrauterine insemination, and assisted reproductive technologies on multiple births

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OBJECTIVE: We sought to quantify the risk of multiple births associated with the use of different modalities of medically assisted reproduction.

STUDY DESIGN: We conducted a case-control study using a birth cohort from 2006 through 2009. This cohort was built with the linkage of data obtained by a self-administered questionnaire and medical, hospital, pharmaceutical, birth, and death databases in Quebec. Cases were pregnancies resulting in multiple live births (*International Classification of Diseases, Ninth Revision*/*International Statistical Classification of Diseases, 10th Revision* codes). Each case was matched, on maternal age and year of delivery, with 3 singleton pregnancies (controls) randomly selected among all Quebec singleton pregnancies. Data on the use of different fertility treatments were collected by a self-administered questionnaire. Multiple logistic regression models, adjusted for body mass index, number of previous live births, ethnicity, family income, place of residence, marital status, subfertility, reduction of embryos, diabetes, metformin treatment, folic acid supplementation, and lifestyle factors, were used to calculate the odds ratios (ORs) and confidence intervals (CIs). We evaluated the associations between each type of fertility treatment (ovarian stimulators used alone, intrauterine insemination [IUI] used with ovarian stimulation, and assisted reproductive technologies [ART]) and the risk of multiple births.

RESULTS: A total of 1407 cases of multiple births and 3580 controls were analyzed. More than half of multiple births following medically assisted reproduction (53.6%) occurred among women having used ovarian stimulation with or without IUI. The use of ovarian stimulators alone and IUI with ovarian stimulation increase the risk of multiple births (adjusted OR, 4.5; 95% CI, 3.2—6.4; and adjusted OR, 9.32; 95% CI, 5.60—15.50, respectively) compared to spontaneous conception. The use of invasive ART was associated with a greatly increased risk of multiple births. Among only the 465 women who used medically assisted reproduction for conception, the use of IUI with ovarian stimulation was associated with an increased risk of multiple births (adjusted OR, 1.98; 95% CI, 1.12—3.49) when compared to ovarian stimulators used alone. Invasive ART were associated with an increased risk of multiple births (adjusted OR, 6.81; 95% CI, 3.72—12.49) when compared to ovarian stimulators used alone.

CONCLUSION: Although the risk of multiple births associated with invasive ART can be decreased by elective implementing of single embryo transfer, special attention should be paid to the greatly increased risk associated with ovarian stimulation used alone or with IUI.

Key words: assisted reproduction, case-control study, epidemiology, in vitro fertilization, intrauterine insemination, ovarian stimulation, risk of multiple births

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Ovarian stimulators are noninvasive fertility treatments used to promote the development and ovulation of >1 mature follicle among subfertile women mainly to increase the likelihood of conception.[1] This treatment can be used alone or in combination with intrauterine insemination (IUI), wherein we increase the numbers of oocytes and sperm together.[2] The ovarian stimulators are also used with other assisted reproductive technologies (ART), such as in vitro fertilization (IVF), which can be used with or without in vitro maturation, intracytoplasmic sperm injection, gamete intrafallopian transfer, and zygote intrafallopian transfer.[3]

Multiple gestations face greater problems than singletons at every stage of pregnancy. Each additional fetus reduces both fetal growth and the duration of gestation, 2 of the most important predictors of fetal and neonatal health.[4] Multiple pregnancies are known to be major risk factor for preterm birth,[5] low birthweight,[5] major congenital malformations,[6] perinatal mortality, and maternal morbidity.[7-9] There is an increase in the number of multiple births in many developed countries.[1,2,7,10] In Canada, the proportion of multiple births among all births has risen from 2.1% in 1991 to 3.3% in 2011.[11] In Quebec, the multiple birth rate per clinical IVF pregnancy was 29.4% in 2009.[12] Multiple embryos transfer during ART treatments and pregnancies in higher maternal ages are factors leading to an overall increase in the incidence of multiple births.[7,13,14]

The use of ovarian stimulators may lead to the multiple follicular developments in stimulated cycles not involving oocyte manipulation. Indeed, clomiphene or gonadotropin medications are first-line treatment used to stimulate the development and ovulation of >1 mature oocyte in ovulatory women with unexplained or age-related subfertility.[1,15,16] Accurate estimation of the ovarian stimulators and IUI use is difficult to determine because these treatments are not currently recorded in national registries. Consequently, their contribution to multiple births became a challenge. Several studies suggest a contribution of ovarian stimulators and/or IUI use to multiple births after medically assisted conception.[1,2,10,17,18] However these studies were not designed to assess the risk of multiple births associated with those treatments.

Quebec is the Canadian province with the second highest number of ART cycles reported[19] and the first government that has introduced a public fertility treatment reimbursement program in Canada.[12] An accurate national assessment of the risk of multiple births associated with the different types of fertility treatments is required to understand the long-term implications of the public funding and for an efficient framing of medical practices.

The objective of this study was to quantify the risk of multiple births associated with medically assisted reproduction, including ovarian stimulators used alone or with IUI or ART. A case-control study was conducted using a database built with the linkage of medical, hospital, pharmaceutical, and birth databases in Quebec together with maternal self-reports on medically assisted reproduction exposures and lifestyle factors.

MATERIALS AND METHODS

Study design and data sources

We conducted a case-control study to quantify the association between medically assisted reproduction and the risk of multiple births. We used data built by a random selection of births with at least 1 live born from January 2006 through December 2008 in the *Régie de l'Assurance Maladie du Québec* (RAMQ) database using *International Classification of Diseases, Ninth Revision* (*ICD-9*) and medical procedure codes related to vaginal or cesarean deliveries. Data on the mothers and children after the end of the pregnancy were obtained with the linkage of data from a maternal self-administered questionnaire with 3 administrative databases: RAMQ, Med-Echo, and *Institut de la Statistique du Québec* (ISQ). The RAMQ provides medical coverage to all 7.8 million Quebec residents and includes information on medical services (diagnoses and procedures) dispensed, emergency department visits, and hospitalizations (date and diagnoses coded using the *ICD-9*). The Med-Echo database records acute care hospitalizations and includes data on the primary and secondary discharge diagnoses (coded with *ICD-9* until the end of 2005 or *International Statistical Classification of Diseases, 10th Revision* since 2006), date of admission, duration of hospitalization, and treatments received during the stay in the hospital. The ISQ database provides demographic information on the mother, father, and baby. Comparisons of ISQ data and medical charts have shown ISQ data to be complete and valid.[20]

Additional data were collected via questionnaire administered to all selected mothers to obtain data on medically assisted reproduction utilization (ovarian stimulators, IUI, ART, and medication use during the fertility treatment) and baseline information on lifestyles, sociodemographic status, weight, and height. Information collected by the questionnaire was linked to databases using the Quebec residents' unique identifier *numéro d'assurance maladie*.

Outcome definition

The births were assigned to the case group if they resulted in >1 live birth to which a validated diagnosis of multiple births (twin births or higher-order multiple births) were assigned at delivery (*ICD-9*: 6441, 6509-6519, 6580-6649, 6680-6699). Each case was matched on maternal age and year of delivery with 3 singleton live births (controls) randomly selected among all Quebec's singleton live births. The multiplicity status (multiple birth or singleton) of each birth was first obtained from the medical records of the RAMQ and then confirmed by the delivery hospitalization found in Med-Echo database. This information was also validated using the ISQ birth registry and finally by the answer of the mother given in the questionnaire. For both cases and controls, we set the index date as the time of delivery.

By completing the questionnaire, a woman gave her consent to participate in the study.