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The relevance of age in female human reproduction – Current situation in Switzerland and pathophysiological background from a comparative perspective

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ABSTRACT

During recent years women tend to postpone childbirth to ages when fertility declines. Consequently, an increasing number of women experiences reproductive difficulties and seeks help by assisted reproductive techniques (ART). To investigate the dynamics of age-related fertility in Switzerland we evaluated data from the nationwide FIVNAT-CH statistics on ART as well as from a subsample receiving ART at the Division of Reproductive Endocrinology, University Hospital Zurich.

Since 2000 the average age of women receiving ART increased from 34.9 to 36.3 years in Switzerland and since 2006 numbers of annual ART cycles augmented steadily. The percentage of women $\geqslant$40 increased from 17.2% in 2007 to 19.6% in 2011. In the Zurich cohort AMH, the number of oocytes retrieved, the number of fertilized oocytes with two pronuclei, the number of embryos with an adequate cell number, clinical pregnancy rates as well as life birth/ongoing pregnancy rates were lower in the age group $\geqslant$40 years, especially when compared to 33 year-old women. In the nationwide sample pregnancy rates decreased from about 45% at the age of 30 to less than 3% at the age of 45; delivery rates declined from about 38% to nearly 0%. In the Zurich cohort percentages of clinical pregnancies declined from 46% in women $\leqslant$34 years to 21% in women $\geqslant$40 years. In the national sample as well as in the Zurich cohort the percentage of miscarriages increased dramatically from 15.4% and 22% in women $\leqslant$34 years to 38.6% and 33% in women $\geqslant$40 years, respectively.

Even in a country with high health standards such as Switzerland fertility is declining with age and ART does not succeed to improve reduced fertility. Rodent and primate models enrich our knowledge on the pathophysiological mechanisms underlying reproductive senescence. As non-infertility specialist physicians as well as the general public are not sufficiently aware of the dramatic reduction of chances for life births in women $\geqslant$40 years, medical counseling as well as schools and media should support the distribution of information future parents need for successful family planning.

1. Introduction

Changes in population demographics, as well as a greater focus on education and careers among women have resulted in increasing numbers of women attempting pregnancy at higher ages. Successful pregnancies in celebrities such as Carla Bruni, Celine Dion, Mariah Carey, or Kelly Preston suggest that pregnancies above the age of 40 can easily be achieved. This impression is cultivated further by a lack of any specific information on whether these pregnancies were conceived spontaneously or with the support of assisted reproductive techniques (ART) and whether pregnancy was induced using an oocyte from the future mother or by egg donation. In addition, advances in ART and control over pregnancy prevention may have caused misconceptions about the present capability to control female fertility (Earle and Letherby, 2007; Perheentupa and Huhtaniemi, 2009). A majority of women incorrectly assumes that fertility decline begins near the age of 40 or gradually concluding at menopause (Daniluk et al., 2012; Lampic et al., 2006; Mac Dougall et al., 2013).

In humans maximal fecundity i.e., the possibility of conception during one menstrual cycle is approximately 30% (Norwitz et al., 2001). This pregnancy rate is much lower than in other species like rodents or rabbits. Due to the current tendency to delay childbirth an increasing percentage of women is confronted with reproductive difficulties. Infertility, which is defined as one year of regular unprotected intercourse without conception, affects approximately 12–15% of couples of reproductive age in Europe. *In vitro* fertiliza-

Abbreviations: ART, assisted reproductive techniques; AMH, antimullarian hormone; FSH, follicle stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

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tion (IVF) experts agree that the number of infertile European couples trying to conceive via IVF or Intracyctoplasmatic sperm injection (ICSI) will double in a decade (EMBIC, 2012; Gnoth et al., 2003; Wang et al., 2003). Currently, with the exception of France birth rates of European countries are below 2 and in many countries birth rates are lower than 1.5 (Switzerland: 1.47, Germany: 1.41, Italy: 1.4, UK: 1.91) (Worldfacts, 2013). The trend towards birth rates strongly below the population replacement rate, i.e., population decreasing in size and growing older, is most pronounced in industrialized countries, especially in Western Europe, where populations are projected to decline dramatically over the next 50 years, with all the known consequences of manpower shortages and resulting migration (Worldfacts, 2013).

For millions of people the inability to have children is a psychological and a financial tragedy, which creates a tremendous economic and social burden in most European societies. For many couples having children is one of the major goals in life, and failure can be associated with the perception of not being a real woman, guilt, inadequacy, personal suffering, loss of the sense of life and societal repercussions (Cousineau and Domar, 2007). Infertility bears an increased risk for negative psychosocial functioning such as depression and anxiety disorders (Herbert et al., 2010; Ogawa et al., 2011; Wischmann et al., 2009). Approximately 32% of women in the early stages of infertility management seem to be at risk of developing clinically relevant mental health problems (Souter et al., 2002). Infertility diagnosis and treatment are directly and indirectly associated with high expenses for the individual as well as for society. Direct and indirect costs are associated with frequent and time consuming medical consultations, expensive medical procedures, limited success rates leading to repeated treatment attempts, time-off from work etc. Infertility related costs represent approximately 1 billion € per year in Europe alone (EMBIC, 2012). Costs for individual couples in Europe are around 10% of annual household expenditures (Collins, 2002).

It is therefore important that health care professionals as well as couples are aware of the epidemiological data and underlying pathophysiological mechanisms of reproductive senescence. A comparative approach might help to better understand such mechanisms (Wu et al., 2005). Aging-related decline in female fertility is a common phenomenon in older women and in females from many other long-lived mammalian species (Keefe, 1998). It is characterized by a progressive decline in fertility attributed to loss of follicles from the ovary, decrease in oocyte quality, age-related defects in the uterus and changes in the neuroendocrine axis. These events are noted in women, non-human primates and rodents (Bellino and Wise, 2003; Danilovich and Ram Sairam, 2006; Shively and Clarkson, 2009). Non-human primate and rodent models are the most established models in research on fertility and aging.

Because of reproductive difficulties, an increasing number of couples seek help via ART. Modern ART i.e., IVF or ICSI have dramatically changed the chances for successful reproduction. However, current success rates for young couples with a female partner below 35 are around 50% in well-functioning centers (DIR, 2012a; FIVNAT, 2012). This is a good success rate, taken the short history of ART, but it is still far away from 100%. In causes of infertility related to severe tubal damage or male factors ART have dramatically improved the prognosis. Unfortunately, even the widespread use of IVF/ICSI will not be able to significantly improve fertility loss caused by aging (Leridon and Slama, 2008).

It was the aim of the presented study to investigate the current situation with regard to age and fertility in Switzerland by (i) analyzing the development of the number of women requesting ART during recent years, (ii) comparing ART treatment in women below and above the age of 40 and (iii) investigating the differences in fertility treatment results between women $\geqslant$40 and below 40.

2. Materials and methods

2.1. Study design

The study is designed as a cohort study presenting data from the nationwide statistics on ART (FIVNAT-CH) as well as a subsample treated at the Division of Reproductive Endocrinology, University Hospital Zurich, Switzerland.

2.2. Study group

The present evaluation includes two study groups: to get an overview of the latest development of fertility treatments in relation to maternal age in Switzerland, we show data from the Swiss national register for fertility treatments (FIVNAT-CH). Then we present data from 120 patients treated between 2010 and 2012 at the Division for Reproductive Endocrinology, Zurich, Switzerland to gain more insight into the chances for successful outcome of IVF/ICSI in different age groups of women.

2.3. ART

The 25 fertility centers in Switzerland have individual strategies to deal with requests for treatment in women above the age of 40. Therefore entry criteria, age limits and treatment protocols vary between centers.

In the Division of Reproductive Endocrinology, Zurich Switzerland all women investigated prior to ART receive a general health check and a gynecological examination focused on those aspects relevant for a future pregnancy. Diseases interfering either with a successful pregnancy or with the ability, to care for the future child until the age of 18 (as requested by the Swiss law), are diagnosed and treated by competent specialists. In addition to the patients' history, hormonal parameters such as FSH, AMH and TSH are used to investigate basic hormonal function. Further parameters such as LH, E2, PRL, androgens (i.e., testosterone, androstendione and DHEAS), cortisol, 17α-hydroxy-progesterone and endocrinological tests are performed when indicated. To maximize specificity FSH and androgens are determined between cycle day 2–4 in women refraining from any hormonal treatment, including oral contraceptives. Infectious diseases such as hepatitis B, C, HIV and *Chlamydia trachomatis* are tested in both partners. Semen analysis is used to get information on male fertility. In case of reduced male fertility meticulous andrological and urological examinations are performed to maximize the chances of pregnancy. The integrity of the uterine cavity is verified either by hysterosalpingography or by hydrosonography, if timed intercourse or intrauterine inseminations immediately have to be excluded as a potentially successful fertility treatment, based on the sperm tests.

Since approximately 1995 the Division of Reproductive Endocrinology accepts women above the age of 40 for treatment. With the increasing success rates of IVF/ICSI treatment and an increased demand in this age group, the age limit was continuously raised to the 43rd birthday. Women $\geqslant$40 years must have FSH levels below 10 IE/l to receive IVF/ICSI. In addition to FSH, AMH and antral follicle count are used to evaluate current fertility reserve. ART treatment is discussed in cases of tubal pathology, male pathology, endometriosis ASRM III/IV and/or idiopathic infertility.

In the Division of Reproductive Endocrinology, Zurich, the long protocol, a modified short protocol or a GnRH antagonist protocol is performed to prepare for IVF or ICSI. To optimize chances for a successful pregnancy, a retrieval of 5 to 15 oocytes is aimed for (Timeva et al., 2006). Follicular development during ovarian stimulation is monitored by transvaginal ultrasound and serum estradiol. When at least two follicles have reached 18 mm and one