

European, U.S. Fertility-Treatment Trends Diverge

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COPENHAGEN — The science is the same, but when it comes to the approach, European and U.S. fertility treatments are starting to branch out in different directions.

The latest (2002) figures from the European IVF Monitoring Program, which includes data from 24 countries, show that the overall pregnancy rate per trans-

fer for in vitro fertilization (IVF) and intracytoplasmic sperm injection is just below 30%, compared with about 35% in the United States, reported Dr. Anders Nyboe Andersen at the annual meeting of the European Society of Human Reproduction and Embryology.

But where the Europeans really differ is in their multiple birth rate—which already is significantly lower than that of the United States and is falling faster.

Of all IVF births in Europe in 2002, 1.3%

were triplet births, down from 3.6% in 1997. That's in stark contrast to the U.S. rate, which currently is 3.8%, down from 7% in 1996.

But it is the rate of twins in IVF births that fertility experts focus on most. That rate stands at 23.6% in Europe, compared with 31.6% in the United States.

The widespread adoption of elective single embryo transfer (eSET) in Europe is the driving force behind the lower multiple pregnancy rate, commented Dr. An-

dersen, coordinator of the European IVF Monitoring Program and head of the fertility clinic at the Rigshospitalet at Copenhagen University Hospital.

Although there is a wide variation in embryo transfer policies across European countries, 70% of all European embryo transfers involved just one or two embryos in 2002. After 2003, when the Swedish government legislated further restrictions, 70% of all Swedish transfers were elective single embryo transfers, reported Dr. Karl Nygren, an ob.gyn. at Sofiahemmet Hospital in Stockholm.

In the United States in 2002, the eSET rate was 1.2%, up from 0.8% the year before, according to Eric S. Surrey, M.D., president of the Society for Assisted Reproductive Technology (SART).

Recent guidelines released by the American Society for Reproductive Medicine, of which SART is an affiliate, suggest that priority for eSET should be given to patients with "the most favorable prognosis" (Fertil. Steril. 2004;82:773-4), and it is important to consider that the most recent eSET figures predate the new guidelines, Dr. Surrey told this newspaper.

"Any impact of this recommendation would not be seen until the 2005 outcome data," he said. At the meeting, when Dr. Andersen was asked why IVF birth rates remain consistently higher in the United States than in Europe, he said that it is too easy to focus exclusively on the fact that Americans transfer more embryos.

"We have to face the fact that they are doing a pretty good job," he told delegates at the meeting.

A key advantage to the U.S. approach is the trend toward smaller and more highly specialized clinics, where doctors can take a lot of time with each patient. "Perhaps Europe could learn from the United States in this regard," he said. ■



Brief Summary (See Package Brochure for Full Prescribing Information)

Rx only

Plan B® is intended to prevent pregnancy after known or suspected contraceptive failure or unprotected intercourse. Emergency contraceptive pills (like all oral contraceptives) do not protect against infection with HIV (the virus that causes AIDS) and other sexually transmitted diseases.

CONTRAINDICATIONS

Progestin-only contraceptive pills (POPs) are used as a routine method of birth control over longer periods of time, and are contraindicated in some conditions. It is not known whether these same conditions apply to the Plan B® regimen consisting of the emergency use of two progestin pills. POPs however, are not recommended for use in the following conditions:

- Known or suspected pregnancy
- Hypersensitivity to any component of the product
- Undiagnosed abnormal genital bleeding

WARNINGS

Plan B® is not recommended for routine use as a contraceptive.

Plan B® is not effective in terminating an existing pregnancy.

Effects on Menses

Menstrual bleeding patterns are often irregular among women using progestin-only oral contraceptives and in clinical studies of levonorgestrel for postcoital and emergency contraceptive use. Some women may experience spotting a few days after taking Plan B®. At the time of expected menses, approximately 75% of women using Plan B® had vaginal bleeding similar to their normal menses, 12-13% bled more than usual, and 12% bled less than usual. The majority of women (87%) had their next menstrual period at the expected time or within 7 days, while 13% had a delay of more than 7 days beyond the anticipated onset of menses. If there is a delay in the onset of menses beyond 1 week, the possibility of pregnancy should be considered.

Ectopic Pregnancy

Ectopic pregnancies account for approximately 2% of reported pregnancies (19.7 per 1,000 reported pregnancies). Up to 10% of pregnancies reported in clinical studies of routine use of progestin-only contraceptives are ectopic. A history of ectopic pregnancy need not be considered a contraindication to use of this emergency contraceptive method. Health providers, however, should be alert to the possibility of an ectopic pregnancy in women who become pregnant or complain of lower abdominal pain after taking Plan B®.

PRECAUTIONS

Pregnancy

Many studies have found no effects on fetal development associated with long-term use of contraceptive doses of oral progestins (POPs). The few studies of infant growth and development that have been conducted with POPs have not demonstrated significant adverse effects.

STD/HIV

Plan B®, like progestin-only contraceptives, does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Physical Examination and Follow-up

A physical examination is not required prior to prescribing Plan B®. A follow-up physical or pelvic examination, however, is recommended if there is any doubt concerning the general health or pregnancy status of any woman after taking Plan B®.

Carbohydrate Metabolism

The effects of Plan B® on carbohydrate metabolism are unknown. Some users of progestin-only oral contraceptives (POPs) may experience slight deterioration in glucose tolerance, with increases in plasma insulin; however, women with diabetes mellitus who use POPs do not generally experience changes in their insulin requirements. Nonetheless, diabetic women should be monitored while taking Plan B®.

Plan B® is a registered trademark of Women's Capital Corporation, a subsidiary of Duramed Pharmaceuticals, Inc.

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Drug Interactions

Theoretically, the effectiveness of low-dose progestin-only pills is reduced by hepatic enzyme-inducing drugs such as the anticonvulsants phenytoin, carbamazepine, and barbiturates, and the antituberculosis drug rifampin. No significant interaction has been found with broad-spectrum antibiotics. It is not known whether the efficacy of Plan B® would be affected by these or any other medications.

Nursing Mothers

Small amounts of progestin pass into the breast milk in women taking progestin-only pills for long-term contraception resulting in steroid levels in infant plasma of 1-6% of the levels of maternal plasma. However, no adverse effects due to progestin-only pills have been found on breastfeeding performance, either in the quality or quantity of the milk, or on the health, growth or development of the infant.

Pediatric Use

Safety and efficacy of progestin-only pills have been established in women of reproductive age for long-term contraception. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of Plan B® emergency contraception before menarche is not indicated.

Fertility Following Discontinuation

The limited available data indicate a rapid return of normal ovulation and fertility following discontinuation of progestin-only pills for emergency contraception and long-term contraception.

ADVERSE REACTIONS

The most common adverse events in the clinical trial for women receiving Plan B® included nausea (23%), abdominal pain (18%), fatigue (17%), headache (17%), and menstrual changes. The table below shows those adverse events that occurred in ≥5% of Plan B® users.

Table 3 Adverse Events in ≥5% of Women, by % Frequency

Most Common Adverse Events	Plan B® Levonorgestrel N=977 (%)
Nausea	23.1
Abdominal Pain	17.6
Fatigue	16.9
Headache	16.8
Heavier Menstrual Bleeding	13.8
Lighter Menstrual Bleeding	12.5
Dizziness	11.2
Breast Tenderness	10.7
Other complaints	9.7
Vomiting	5.6
Diarrhea	5.0

Plan B® demonstrated a superior safety profile over the Yuzpe regimen for the following adverse events:

- Nausea: Occurred in 23% of women taking Plan B® (compared to 50% with Yuzpe)
- Vomiting: Occurred in 6% of women taking Plan B® (compared to 19% with Yuzpe)

DRUG ABUSE AND DEPENDENCE

There is no information about dependence associated with the use of Plan B®.

OVERDOSAGE

There are no data on overdosage of Plan B®, although the common adverse event of nausea and its associated vomiting may be anticipated.

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ICSI Procedures Rise in Europe

For the first time in Europe, the number of intracytoplasmic sperm injection cycles exceeded regular IVF cycles; ICSI was used in 52% of all IVF cycles in 2002.

This is similar to the U.S. situation in which ICSI is used in 53% of cycles.

There are probably many reasons for the shift. "One of them could be that the relative causes of infertility are shifting," Dr. Andersen said.

There are now fewer severe tubal problems because of better protection against STDs, while there is growing evidence male subfertility may be increasing as a result of environmental pollutants, he said. Also, many couples who previously might have used artificial insemination with donor sperm are now opting for ICSI.

Finally, since the procedure was first introduced in 1992, clinics have become more familiar and more skilled at performing it, thus making it more widely available.