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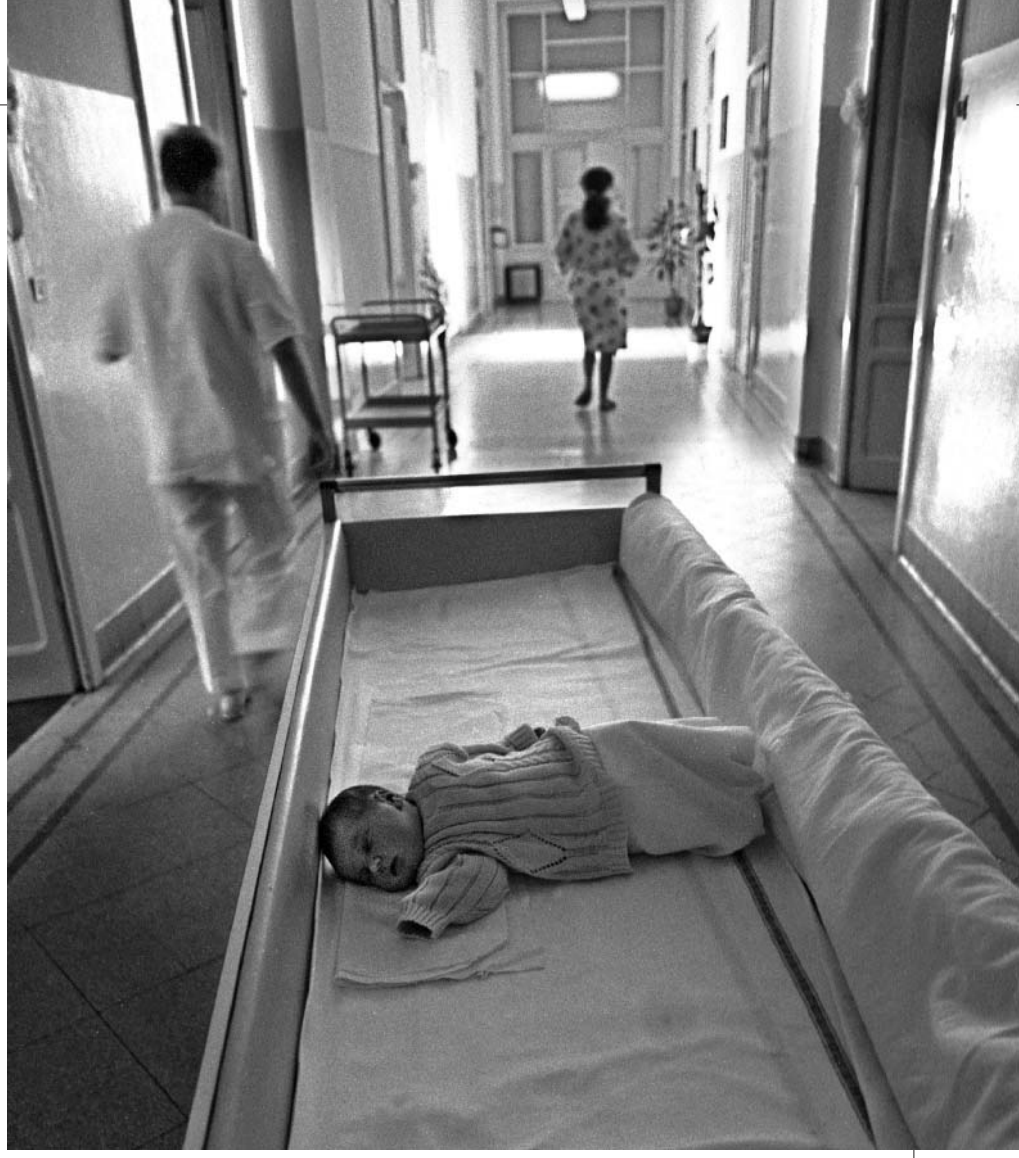


Slow day in an Italian maternity ward. Low birth rates promise future population decline.

The fertility riddle

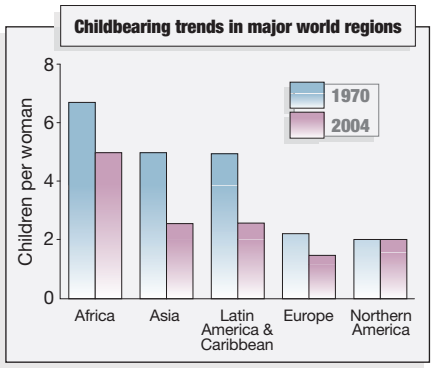
Across the developed world, birth rates are plummeting. Is this just a social phenomenon, or is our biological fertility also declining? We don't yet know, and that is worrying, says Declan Butler.

If current trends continue, Japan will be deserted by the middle of the next millennium. The nation's birth rate is so low that its population will peak in 2006 and decline thereafter[1] — raising the prospect of economic chaos as a greying population overwhelms its pension and healthcare systems. It's a similar story in South Korea, Italy, Spain and across most of Eastern Europe. In only four industrialized countries are women, on average, having the two children needed to sustain the population[2] (see chart).

This demographic change is mostly the result of a social climate in which couples are choosing to have fewer children, or none at all. But might something more sinister be going on, such as environmental pollution or sexually transmitted diseases causing a decline in male or female fertility?

"We must take the possibility seriously, but it's too early to be alarmist," says Henri Leridon, who heads the Laboratory of Epidemiology, Demography, and Social Sciences at the University of Paris XI.

What is alarming is that few credible data have been collected on the issue. If our biological fertility is on the slide, it's happening against a background of scant interest from research organizations. But there are reasons to be concerned. For one thing, women's fertility declines with age — and this means that the trend to start families later is bound to create problems. Looking ahead, the expansion of *in vitro* fertilization may create a cohort of adults who have inherited their parents' fertility problems.



SOURCE: UN

The shift towards having more sexual partners in a lifetime carries another infertility risk: sexually transmitted diseases. Some 5% of Americans of reproductive age are infected with the bacterium *Chlamydia trachomatis*, a major cause of female infertility — which is rarely diagnosed as it produces no obvious symptoms[3]. "That's an epidemic," says Peter McGovern, a fertility specialist at the University of Medicine and Dentistry of New Jersey in Newark.

Fertility experts are also concerned that another epidemic — of obesity — may bring infertility. Many severely obese women fail to ovulate, even if they report regular menstrual cycles. And obesity is linked to polycystic ovary syndrome, an important cause of infertility in which ovarian follicles fail to mature. Up to 10% of US women are thought to have this condition; it's hard to be sure of the figure because of disagreements over its diagnosis[4]. "But as it's related to obesity, we are going to see more of it," McGovern predicts.

Born that way

Smoking, alcohol consumption and a range of other lifestyle factors can all reduce a couple's ability to conceive, usually affecting women more severely than men. Most of these factors act through hormonal pathways, so understanding these interactions poses a major challenge to endocrinologists.

But one of researchers' biggest obstacles is that our fertility is mainly determined by the environment we inhabited in the womb[5]. A woman's stock of eggs is defined by the number and maturity of her ovarian follicles when she herself was an embryo. Normal fetal follicular development depends on the mother's diet and other lifestyle factors, including her exposure to chemicals.

Next in line: fertility problems may be passed from one generation to the next.

D. ANSCHUTZ/IMAGE BANK/GETTY

Adult male sperm count and quality is determined largely by the development of sperm-nurturing Sertoli cells in the embryonic testes. This depends heavily on exposure to sex hormones in the womb, which again is influenced by the mother's lifestyle and other environmental factors.

Prospective parents

So if fertility specialists are to make sense of trends in biological fertility, ideally they should conduct prospective studies relating these environmental factors to the fertility of the next generation in the decades to come.

Until now, most information has come from retrospective studies, in which parents are asked about their lifestyle and environment at the time when they were having children, including their exposure to toxic chemicals. "Trying to measure exposures 30 years ago is very difficult," observes Stewart Irvine, an expert on male infertility at the UK Medical Research Council's Human Reproductive Sciences Unit in Edinburgh.

Such problems have bedevilled attempts to find out whether pollution is reducing sperm counts and sperm quality (see page 48). It has been difficult even to determine whether there really is a decline. Semen samples vary enormously in sperm density and quality, within and between individuals, so you need large sample sizes to detect any drop in sperm counts. But it is hard to recruit volunteers to give sperm, and those who do sign up often have a vested interest: their own fertility problems. "You really can't get representative population samples," complains Michael Joffe, an epidemiologist at Imperial College London, who studies fertility trends.

Women's fertility should be causing as much concern as men's, but it has attracted less attention. In the United States, a headache for researchers is that medical insurance often does not cover treatment for female infertility. "This means doctors usually code it as endometriosis or fibroids, or something, so that patients can get insurance coverage," says McGovern. "This has a big impact on the data. It's the elephant in the room."

Experts are increasingly using 'time to pregnancy' studies to investigate infertility. In these, they ask couples having unprotected sex how long it took them to achieve a pregnancy, and to relate this information to factors that might influence fertility.

So far, most of these studies have been retrospective, and have raised as many questions as they have answered. Joffe, for example, gave 1,540 Britons aged 16–59 a questionnaire, and found that fertility seems, if anything, to be increasing[6]. The percentage of couples taking longer than one year to get pregnant fell from 21% in 1960–65 to just 10% in 1991–93.

Another study[7], based on the US National Survey of Family Growth, a survey of thousands of Americans conducted every few years, suggested that fertility declined between the early 1980s and the mid-1990s. The authors attributed this to women starting their families at a later age.

> "Studies need large samples. But it is hard to recruit volunteers to give sperm, and those who do often have a vested interest: their own fertility problems."

Joffe is preparing to publish a follow-up study of 40,000 subjects. Shanna Swann, a reproductive epidemiologist at the University of Missouri-Columbia, will soon publish a meta-analysis of fertility studies conducted over the past five decades. But Leridon cautions against studies that rely on recalling information about past pregnancies. "These surveys don't give clear evidence," he says.

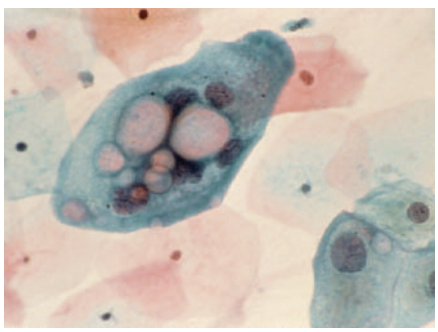
What is needed, argue many experts, are studies in which couples are recruited before they conceive[8]. To detect the effects of factors such as environmental pollutants, these studies should record, for instance, frequency of intercourse and timing of ovulation.

Given the difficulty and cost, such studies are few. This has led Roger Short, a reproductive biologist at the University of Melbourne in Australia, to suggest monitoring the incidence of non-identical twins as an alternative strategy[9]. This is a reasonable measure for a combination of male and female fertility, he argues, because it reflects the frequency of double ovulation, the probability of fertilization, and the survival of embryos.

Care would be needed to exclude women taking drugs to stimulate ovulation, and those whose ovulation has been depressed by the prolonged use of oral contraceptives. But it shouldn't be difficult, Short suggests, for researchers to use twins to make inferences about changes in fertility.

Maybe so, but experts aren't betting that this short cut will determine whether our biological fertility is in decline. If governments want the answer to a question that could have profound demographic and economic consequences, argues McGovern, they must provide substantial increases in funding. Ultimately, the science of human fertility is hampered by a chronic lack of research into basic reproductive biology, epidemiology and toxicology — in particular in the developing embryo.

The bottom line, says Irvine, is that studies addressing trends in fertility are "simply very difficult to do. Sometimes I wish I'd chosen to work on something else." ■



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Invisible epidemic: *Chlamydia* infection is a major cause of female infertility.

Declan Butler is *Nature*'s European correspondent.

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