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What Did We Learn in the Last 50 Years and what are Our Expectations for the Future of Reproductive Medicine

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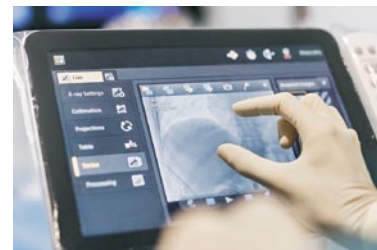
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What Did We Learn in the Last 50 Years and what are Our Expectations for the Future of Reproductive Medicine*

B. Lunenfeld

■ Introduction

Till 1962, we only had IUI for male factor infertility, surgical procedures for tubal obstruction and ovarian wedge resection for PCO. These 3 techniques helped about 5% of childless couples to have their genetic child. In 1954, we were privileged to show that an extract of menopausal urine could stimulate ovarian activity however this was met with skeptics as demonstrated by **F. Stabler** in 1954 [1] where he wrote “*I think I can say that I know of no hormone available to me that will make a woman ovulate naturally*”. By 1978 we had most of the drugs available to manage hormonal causes in both male and female infertility. In 1978 **R. Edwards** and **P. Steptoe** reported the birth of the first human IVF [2] in a natural cycle. This was followed by **H. Jones** et al. reporting in 1981 the first series of children born after IVF using the method we described earlier namely hMG to stimulate the development of multiple follicles and hCG to obtain ovulation [3]. This method with some modification remained the standard method for IVF till today.

International Organizations like the G-Club, founded in 1954, IFFFS, and regional organizations like ASRM (USA), ESHRE (Europe), and ASPIRE (Asia) helped to educate and train scientists, physicians and supporting profession to optimize our procedures and hopefully will continue to do this.

The pharmaceutical industry has helped us to have highly potent and safe preparations. Biochemists, diagnostics and engineers and medical equipment gave us the tools to diagnose and manage our patients.

■ So what did we learn in the last 50 years?

That:

- **90% of infertile couples** can have their genetic child if they are diagnosed and treated before the age of 35
- **Life Birth Rates (LBR)/aspiration in (IVF cycles) increased** significantly, due to better methods and culture media
- **LBR/initiated IVF cycles increased** significantly, due to better protocols (Fig. 1). However there are still large variations in LBR worldwide some due to age distribution (Fig. 2). Even when age was taken into consideration variations still remained considerably (Tab. 1). This is most probably due to differences in protocols used and number of embryos transferred (Tab. 2).

- **Multiple deliveries decreased** significantly, due to the number of ET transferred (Fig. 3).
- **GnRH analogues** administered from the mid-luteal phase of the prior cycle until the completion of the COS process (long protocol) by inhibiting endogenous LH surges has played an important role in improving ovulation inducing protocols This approach reduced cycle cancellation rates (as high as 35% before the introduction of GnRH agonists)
- **Hyperstimulation rates** in ART decreased significantly mostly due to the greater experience and better consistency in gonadotropin stimulation and the use in high risk patients of GnRH antagonists permitting ovulation induction with GnRH agonist instead of hCG, or cryopreserving the embryos and transferring them in a later cycle (Fig. 4).

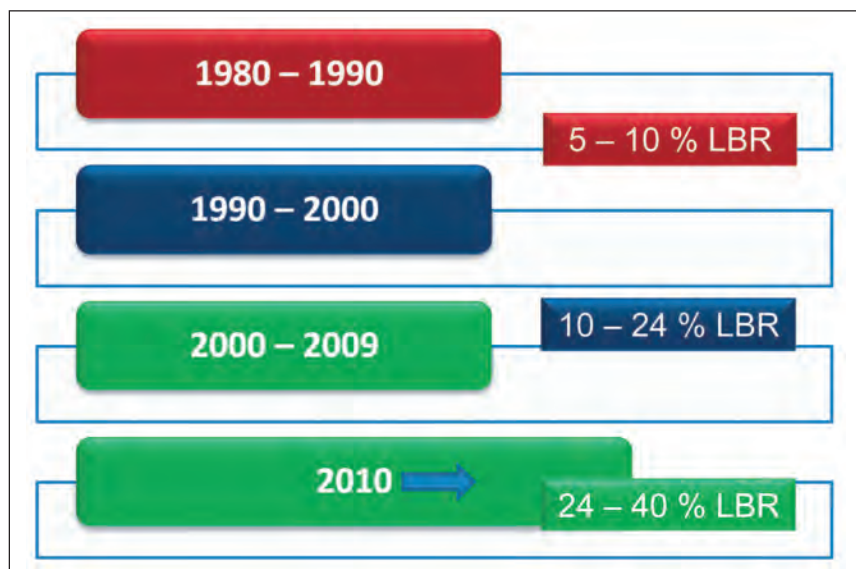


Figure 1. Success in ART as measured by LBR: Improved since 1981 from 5–10% to 24–40%.

* Brief manuscript, based on a recent lecture of Prof. Bruno Lunenfeld.

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Table 1. Protocols for women < 35 (10–20 pmol AMH AFC 5–15) and yield of oocytes.

Conventional IVF	8–15 oocytes LBR = 20–41%	GnRH agonist/antagonist FSH/hMG 150–300 IU FSH/LH 150–300 IU
Mild IVF	2–7 oocytes LBR = 15–25%	CC/FSH/hMG low dose
Modified natural cycle (IVF)	1 oocyte LBR = 5–10%	hCG only +GnRH antagonist with FSH/hMG or FSH/LH add back
Natural cycle	1 oocyte LBR = 3–6%	

Table 2. LBR rates in JP, UK, Australia and USA according to age. A live birth was defined as the birth of at least one live-born baby beyond 20 weeks' gestational age who survived for at least 28 days. Live births were counted as birth events (i. e. a twin or triplet live birth was counted as one live-birth event).

Age	JAPAN LBR/ITT	UK LBR/ITT	Australia/NZ LBR/ITT	USA LBR/ITT
< 35	15%	33.1%	37.8%	41%
35–39	10%	23.25%	18.0%	27%
40–44	4%	8.5%	6.8%	12,6%

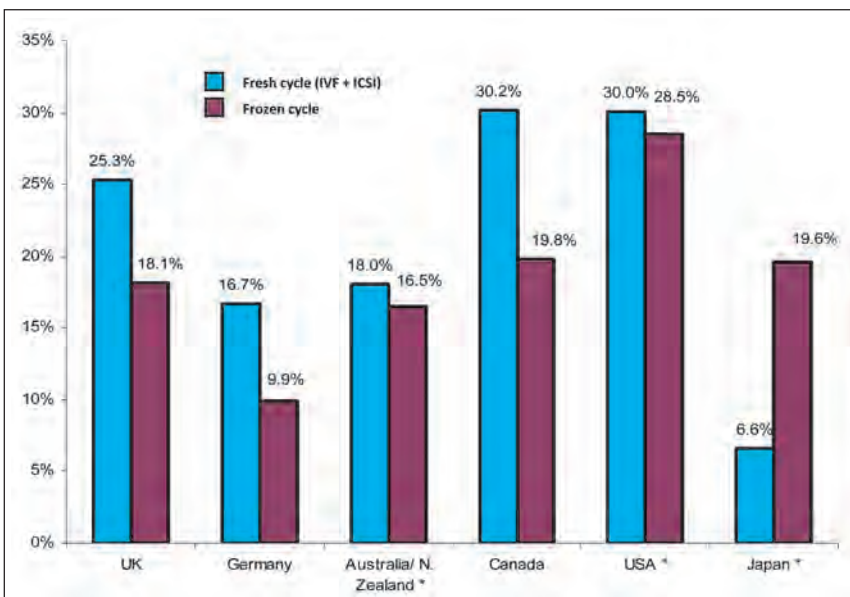


Figure 2. Rate of live-birth delivery per initiated cycle (variations due to age distribution and protocol use). Sources: Europe, UK, Germany: 2007 results from ESHRE [De Mouzon et al., 2012]; Canada: 2009 results from Canadian ART register (2011); USA: 2009 results from US CDC report (2011); Japan: 2008 results from Japan Society of Obstetrics & Gynecology; Australia/New Zealand: 2009 results from Australian Institute of Health and Welfare report, 2011.

cancer, and patients with thrombophilia to avoid the risk of thrombosis following ovarian stimulation and has also been proposed for avoiding hyperstimulation in high risk patients (PCOS)

- We now have tools such as Antral-Follicle-Count by sonography and Anti Muellierian Hormone estimations (AMH) to **predict dose and treatment protocols**.
- Preimplantation genetic diagnosis (PGD) gained an important role in the prevention of genetic diseases. More indications have recently been applied such as aneuploidy screening, HLA typing and mitochondrial disease.

We still have a long way to go till our goal a child for every couple who desires it, will be achieved.

■ What are our expectations for the future of reproductive medicine?

- We now need to discover **objective biomarkers** [4] of ovarian response including a combination of genetic, hormonal and functional markers that will help us define the right **individual treatment** for the right patient to reduce cancellations due to OHSS and poor response, while maximizing the chances of achieving each time the birth of a single healthy child, not only in ART patients but also in uniovulatory patients of Groups WHO I and WHO II
- Evaluation of gametes viability, evaluation of embryos implantation potential and uterine receptivity potential are today still subjectively defined. **To improve the efficiency of the system** we need to discover ways of move away from empirical subjective systems and move to objective repeatable and validated biomarkers of ovarian response, of gametes health and viability, of embryo implantation potential and of uterine receptivity!
- **The Aging Ovary:** As the ovary ages, there is a constant decline of recruitable follicles and age-related quality declines in oocytes. Parallel to the decrease of follicles there is a decrease in AMH and AFC permitting to make the diagnosis of poor response and permitting to adapt an individualized

- We now have **safe products** with **batch to batch consistency**. The most significant advantage of rec-hFSH over urinary-derived hFSH is that it permits FSH to be quantified reliably by protein content (mass in mg) rather than by biological activity; this indication of purity offers optimal risk reduction as well as superior quality assurance and batch-to-batch consistency. The coefficient of variation for an in vivo bioassay is typically 20%, compared with 2% for

- physico-chemical analytical techniques such as size exclusion high-performance liquid chromatography (SE-HPLC)
- The availability of **cryopreservation of sperm, embryos, ovarian tissue and oocytes** permitted fertility preservation in male or female cancer patients or in women who desire to postpone child bearing for socio economic or other reasons
- **The development of in-vitro maturation (IVM)** is helping patients with

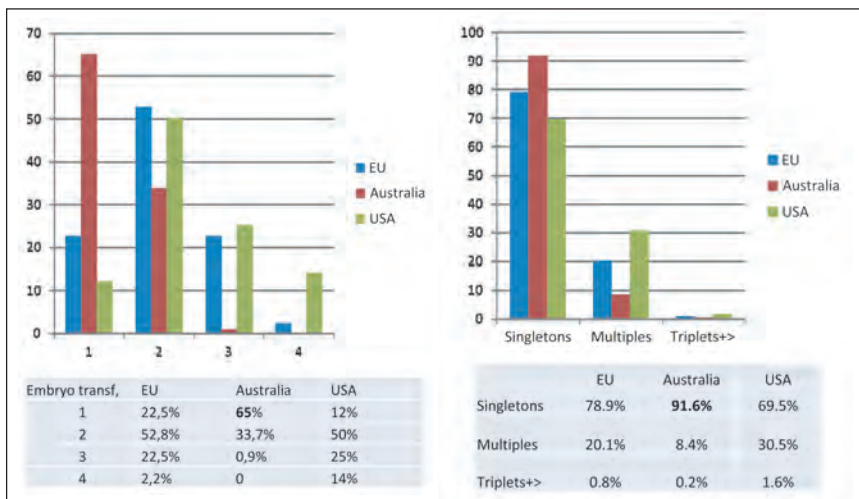


Figure 3. Number of ET transferred and resulting multiple deliveries. During 13 years (1997–2009) in Europe multiple delivery rates declined by 32% and triplets by 78%. Source: European registry by ESHRE 2008 (CDC 2010); Assisted reproductive technology in Australia and New Zealand 2009.

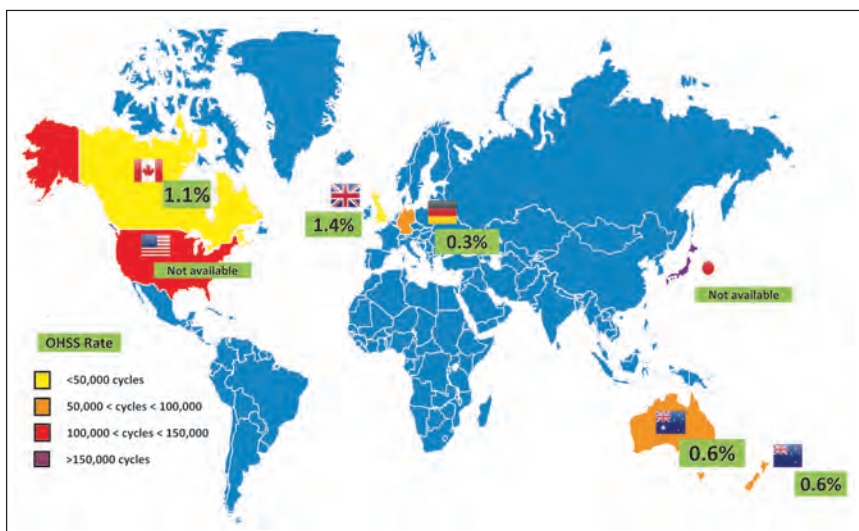


Figure 4. Rate of OHSS per ART cycle initiated. Sources: Europe, UK, Germany: 2007 results from ESHRE [De Mouzon et al., 2012]; Canada: 2009 results from Canadian ART register (2011); USA: 2009 results from US CDC report (2011); Japan:2008 results from Japan Society of Obstetrics & Gynecology; Australia/New Zealand: 2009 results from Australian Institute of Health and Welfare report (2011).

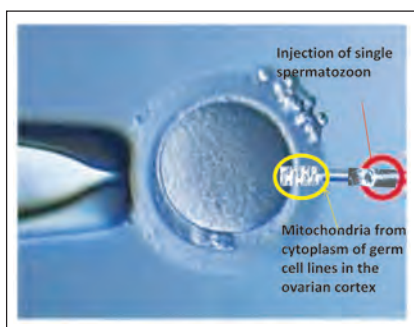


Figure 5. Injection of autologous purified mitochondria. Oocyte stem cells are purified from the other cells, in the ovarian cortex and the mitochondria is extracted from the stem cells. In order to satisfy legal, ethical and scientific criteria the source of the mitochondrial activity must meet two requirements: the mitochondria must be obtained from the same individual as the oocyte (autologous) and the mitochondria must be germ line quality (undamaged and free of mutations).

protocol. As to the decreasing egg quality donation of autologous mitochondria from germ line cells which as recently shown exist in the ovarian cortex might be helpful to overcome age-related quality declines in oocytes (Fig. 3).

- We also need to discover: 1) ways of **protecting the primordial follicles** during their latent time in the ovary to avoid ageing 2) ways to **control the number of follicles to grow** in each cycle by turning on/off dormant follicles.
- **Human pluripotent stem cells** are characterized by the ability to renew indefinitely in culture while retaining their capacity to differentiate into most, if not all, cell types [5]. Human

embryonic stem (hES) cells are pluripotent stem cells derived from the inner cell mass of the blastocyst-stage embryo. These preimplantation embryos generally exist in at in vitro fertilization (IVF) clinics and are donated to research by individuals under informed consent. Of particular interest for the study of disease are stem cell lines produced from embryos discarded after PGD because they were identified to carry disease-associated mutations. Such disease-specific stem cell lines would in turn be expected to carry the disease genes responsible for the condition and could prove useful for clinically informative models for mechanistic studies and therapeutic drug discovery.

- **An emerging application for PGD** is to prevent genetic conditions that manifest in adulthood. A feasible strategy including whole genome amplification followed by direct mutation detection combined with haplotyping. Utilizing haplotyping increases the efficiency of PGD diagnosis as well as confirming the genetic diagnosis. It reveals the parental origin of each inherited chromosome [6]. The number of genetic disorders for which PGD can be used also continues to climb steadily with estimates at 170 different genetic disorders.
- We need to encourage our colleagues to **prevent infertility**. Prevention is cheaper than cure, “even using the mildest stimulation protocols”. It may be less profitable to the service providers and pharmaceutical companies but this must not our concern. Prevention of STD by the use of barrier techniques, delaying adolescence pregnancies and unwanted pregnancies by contraception and sex education in schools, may all reduce mechanical causes of infertility for which IVF was created.
- We still need to **create better and safer methods for IVF**. Unfortunately major part of congress programs are filled with these issues. Should we not spend some time and money to prevent the conditions which make IVF necessary?
- ICSI was a blessing, but again we were so impressed with a method that could help nearly all men to have genetic heirs, that we forgot to invest in **andrology**, and in quite a

number of countries positions for andrology in medical school disappear and they are replaced by high grade technicians who will attempt to find a few sperms and will try with sometimes sophisticated method to select the best. Unfortunately investments in the science of andrology almost disappeared.

Let us **promote health education**, fight the global epidemic of obesity, promote

a healthy life style with proper nutrition and physical exercise and help to reduce stress – this might be a very good investment and may decrease hypothalamic-pituitary and metabolic conditions related to male and female sub fertility or infertility. We are privileged to be among those who can bring the joy of parenthood to the childless couples, we must continue to strive to obtain our goal a singleton pregnancies with healthy children to every couple.

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