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In vitro fertilisation

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Summary Approximately 50% of infertile couples will require treatment with some form of assisted conception in order to achieve a pregnancy. In vitro fertilisation (IVF) can be viewed as both a test of reproductive potential, allowing a detailed assessment of oocytes, oocyte sperm interaction and embryo quality, and an effective treatment for most forms of subfertility. The many improvements in IVF treatment since the first baby was born some 27 years ago have occurred as a result of close multidisciplinary collaboration and the practical application of scientific advances in embryology and pharmacology. There have been several important landmarks, including the introduction of drugs for pituitary downregulation and superovulation, the introduction of transvaginal ultrasound scanning for monitoring follicle growth and oocyte retrieval, developments in embryo culture, oocyte donation, and the introduction of intracytoplasmic sperm injection for the treatment of severe forms of male infertility. The pace of change has not slowed: within the past decade, new technologies, including preimplantation genetic diagnosis, the in vitro culture of immature oocytes to viability, and the cryopreservation of oocytes, have widened the scope of clinical problems that can be addressed by IVF-associated technologies. Despite this progress, the majority of IVF cycles still do not produce a viable pregnancy, and the psychological stresses imposed upon couples by assisted conception treatment need to be managed carefully and sympathetically. IVF practice continues to require support from appropriately trained and skilled counselors.

Introduction

The history of human in vitro fertilisation (IVF) is short, effectively beginning with the birth of Louise Brown, the first IVF baby, in 1978. Her conception was the result of a collaboration between Robert Edwards, a scientist from Cambridge with long-standing research interests in human and animal embryology, and Patrick Steptoe, a gynaecologist and laparoscopist from Oldham in Lancashire. Collaboration was essential as Steptoe was able to collect oocytes by the transabdominal needle aspiration of mature follicles under laparoscopic view and Edwards had the necessary laboratory

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skills eventually to achieve the growth of embryos after fertilisation in vitro. The importance of collaboration between disciplines remains as true today as it was in the 1970s.

The birth of Louise Brown was soon followed by the birth of further IVF babies in Australia and the USA. At the time, there was widespread disquiet among both the public and the medical profession concerning the morality, and even legality, of the process of IVF. This debate led to the establishment first of a Voluntary Licensing Authority, and later the Human Fertilisation and Embryology Authority (HFEA), by the UK government. The role and powers of HFEA continue to change as the umbrella of IVF applications continues to grow, and the organisation has been emulated in many countries over the past two decades.

How IVF works

Although 'human' IVF did not come of age until 1978, most of the technological steps had been developed earlier for use in veterinary medicine. The principle of IVF is simple: collect mature oocytes (eggs) from the ovaries, fertilise them in cell culture in the laboratory and replace the embryo(s) into the uterine cavity at such a time in the cycle to ensure a receptive endometrium. However, each step in this model has been refined by decades of experimentation, leading to the quasi-industrial IVF of today.

Stimulation of multiple follicle development

One of Steptoe and Edwards' greatest problems was a shortage of oocytes. They were able to harvest only one or two oocytes in the natural cycle, and frequently, by the time that laparoscopy had been arranged, general anaesthesia induced and surgery undertaken, the follicle had ovulated and the oocyte had been lost in the pelvis. Success rates were therefore low. In order to improve the chances of having embryos for transfer, the embryologist needed more oocytes and the clinicians needed to be certain that premature ovulation would not occur.

Gonadotrophins

Gonadotrophins were first isolated from the urine of pregnant women by Aschheim and Zondeck in 1927. Three years later, Zondeck reported their presence in the urine of menopausal women. However, the first use of gonadotrophins for inducing multiple ovulation utilised extracts of human pituitary tissue collected at postmortems. Many pituitaries were needed to obtain sufficient extract to treat a single patient, and much later, in the 1980s, pituitary-derived gonadotrophins were found to have transmitted Creuzfeld–Jakob infection in a small number of cases. It was not until 1947 that human menopausal gonadotrophins were first extracted from urine, creating the possibility of a readily available pharmaceutical source for widespread clinical use. More recently, recombinant follicle-stimulating hormone (FSH) and luteinising hormone (LH) have been made available following transfection of the genes for the alpha and beta chains of human FSH or LH into Chinese hamster oocyte cell lines, producing large amounts of glycosylated FSH and LH without the need for collection and extraction from human urine.

Treatment with gonadotrophins was initially by intramuscular injection of an impure fraction containing both LH and FSH. In time, purified urinary FSH and later recombinant FSH became available for subcutaneous injection. Gonadotrophin injection encourages the development of a cohort of mature follicles in a single stimulation cycle, overriding the physiological processes of follicle selection and dominance. Egg collection could yield anything up to 40 oocytes after 10–14 days of daily injection.

In the early days of superovulation, ultrasound had not developed sufficiently for the assessment of follicle growth, and clinicians could obtain an approximate measurement of ovarian response to treatment only by the daily measurement of urinary oestrogens, a process that was time-consuming and inaccurate. Poorly controlled ovarian stimulation caused rapid rises in circulating oestrogen concentration that triggered premature LH surges with premature ovulation and a loss of oocytes before egg collection was undertaken. Therefore, having established a means of obtaining multiple oocytes, attention turned to the pharmacological control of pituitary responsiveness to rising oestradiol concentrations in order to prevent premature LH surges.

GnRH analogues with agonist

Native gonadotrophin-releasing hormone (GnRH) is a simple decapeptide with a very short half-life (approximately 3 min) owing to enzymatic cleavage