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SYMPOSIUM: THE HISTORY OF THE FIRST IVF BIRTHS

The Oldham Notebooks: an analysis of the development of IVF 1969–1978. III. Variations in procedures

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Kay Elder joined Bourn Hall in 1984 as Clinical Assistant to Patrick Steptoe, directing the Out-Patient Department from 1985 to 1987. Her scientific background as a research scientist at Imperial Cancer Research Fund prior to a medical degree at Cambridge University naturally led her to Bob Edwards and the IVF laboratory, where she worked as a senior embryologist from 1987. A programme of Continuing Education for IVF doctors, scientists and nurses at Bourn Hall was established in 1989, which she directed for 16 years. During this period she also helped to set up and run two Master's degree programmes in Clinical Embryology, and she continues to mentor and tutor postgraduate students of Clinical Embryology at the University of Leeds. In her current role as Senior Research Scientist at Bourn Hall she co-ordinates research collaborations with the MRC Laboratory of Molecular Biology in Cambridge and the MRC National Institute for Medical Research in Mill Hill.

Abstract A survey is presented of the various technical and scientific challenges that had to be met during the 10-year period before the first successful live birth after IVF and embryo transfer was achieved, and the approaches used to meet these challenges is discussed. Records dated from January 1969 to July 1978 indicate that a minimum of 282 women were involved in 495 cycles scheduled for laparoscopic oocyte recovery, of which 457 cycles (92%) proceeded to attempted egg collection. A total of 1361 eggs were recovered over 388 cycles, of which 1237 (91%) are recorded as having been inseminated in 331 (85%) of these cycles. Approximately 221 embryos were described in 165 (43%) of the 388 cycles. A total of 112 embryo transfers were attempted, which resulted in five clinical pregnancies with two live births. This paper discusses the ways in which hormonal stimulation of follicle growth to the pre-ovulatory stage was varied, and the endocrine monitoring of these variations in blood, urine and follicular fluid, as well as their influence on egg recovery and fertilization rates. Variations in media composition and preparation are also described. It is concluded that, whilst driven by scientific reasoning, the approach adopted in trying to achieve successful IVF was empirical rather than evidence-driven.

KEYWORDS: blastocyst development, early pregnancy, human embryo culture, luteal phase abnormalities, natural cycles, pregnancy losses, stimulated follicular maturation

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Introduction

Louise Joy Brown was born on 25 July 1978, an event that has had a major impact on science, medicine and society (Franklin, 2013). In the two preceding papers, we reported on our analysis of research notes spanning 1969 to 1978 covering the period when Edwards, Steptoe and Purdy were working in Oldham and Cambridge towards this achievement (Elder and Johnson, 2015a), and on the numbers of treatment cycles involved and their outcomes (Elder and Johnson, 2015b). In this paper, we consider the evidence relating to variations in key aspects of the procedures that Edwards, Steptoe and Purdy attempted in order to overcome the numerous technical, scientific, practical and logistical challenges they faced. An overview of some of the many problems that had to be addressed and overcome (Edwards and Steptoe, 1974) is presented in Table 1. We present a historical perspective on the steps taken to resolve these issues. The data for this report are taken primarily from the two sets of notebooks, L0–L9 and H1-H4, H7-H9, as described in Elder and Johnson (2015a), supplemented with additional material from the Edwards' archive, which are referenced as RGE1, 2 etc., followed by the date.

Results and discussion

Laparoscopic oocyte recovery procedure: follicle aspiration, ovulation induction and timing

Having realized that in-vitro matured oocytes were not competent to develop as embryos, preliminary attempts at laparoscopic oocyte recovery (LOR) may have already commenced late in 1968, as mentioned in Edwards and Steptoe's 1980 account in their volume *A Matter of Life* (Edwards and Steptoe, 1980, pp.80–81) and reported in Edwards et al. (1969, p.635; published on 15 February, submitted December, 1968). During 1969 the main emphasis was on improving the timing and technique of laparoscopy and recovery of eggs after triggering oocyte maturation. Follicles were initially aspirated using a syringe and needle, but this method was found to be unsatisfactory (Steptoe and Edwards, 1970). In September 1969 a "new suction gadget – boiled" was introduced (Figure 1), which had a bypass valve that allowed the assistant to control suction, with the result that clearer follicular fluids could be collected. This 'gadget' was then used with variations in suction pressure of 1, 4, 5, 8, 10, 12 cm Hg, before establishing an 'optimum' pressure of no greater than 12 cm Hg, 'since higher pressures may damage the oocytes' (Edwards et al., 1980b; Steptoe and Edwards, 1970, p.684).

Initially, human chorionic gonadotrophin (HCG; Pregnyl, Organon) was administered in order to induce final follicular maturation when an adequate concentration of urinary oestrogens was detected in 24-hour samples (>75 μg/day), usually on day 11 or 12 of the cycle. Although guided by the timing of oocyte maturation *in vitro* (Edwards, 1965), scheduling the laparoscopy was determined mainly by the team's availability and their access to the operating theatre: "HCG was given at an arbitrary time, selected for our own purposes and not because the patient had been fully primed by the HMG" (Steptoe and Edwards, 1970). The dataset for 1969 records that HCG was administered 29–31 hours prior to laparoscopy (See Table 2 and Suppl. Table in Elder and Johnson, 2015b).

Doses of HCG were initially related to the dose of gonadotropin administered for inducing follicular maturation, and varied from 3000 to 12,000 IU (Table 1; Steptoe and Edwards, 1970), 5000 IU being adopted from September 1969 onwards, when "a regimen of three injections of HMG between days 2 and 9, and 5000 IU of HCG on days 9–11 of the menstrual cycle gave the best response" (Steptoe and Edwards, 1970). The interval between HCG and egg collection was also varied, and the duration of this interval was compared with the presence of corpora lutea to confirm whether or not ovulation had already taken place at the time of laparoscopy. The notebooks record that laparoscopy was carried out on days 10–12, with an initial interval between HCG and laparoscopy of 28.75–29.50 h, increased to 29.50–30.00 h from mid-January 1970, and then to 32.0–33.5 h in mid-March 1970 (See Table 2 and Suppl. Table in Elder and Johnson, 2015b). This interval was adjusted for natural cycles during 1978, when the timing of the laparoscopy was set at 15–35 h after detecting the LH surge (Edwards et al., 1980a, p.748 and Table IV). Eggs recovered are described as 'fixed' prior to October 1969, and are presumably those that were studied cytologically and/or chromosomally with many not fully mature at recovery (Elder and Johnson, 2015b, Steptoe and Edwards, 1970).

Table 1 Some of challenges that had to be overcome before the first successful live birth following IVF and embryo transfer was achieved.

Challenge
Technical aspects of follicle aspiration ('new suction gadget')
Ovulation induction
Timing of laparoscopy
Ovarian stimulation
Cycle monitoring
Oocyte culture
Sperm preparation
Insemination procedure: medium, timing
Culture for embryo cleavage: medium, assessment
Technical aspects of embryo transfer, including route of transfer, medium and timing
Luteal support

Follicle stimulation regimes

Two important initial goals were to aspirate oocytes from their follicles just before ovulation was expected, and to have more than one pre-ovulatory oocyte for aspiration. Injection of the gonadotrophic hormones, human menopausal gonadotrophin (HMG) and HCG, was felt to be necessary in order to control the menstrual cycle and regulate follicle growth, oocyte maturation and ovulation (Edwards et al., 1980a, 1980b; Steptoe and Edwards, 1970). Table 2 shows the variations over the years in the stimulation regime used to induce follicular maturation, described in Steptoe and Edwards (1970) as "a priming dose of HMG, followed by an ovulatory dose of HCG". In the absence of any knowledge about the potential ovarian response, and in order to avoid the risk of ovarian hyperstimulation syndrome, low doses