# The importance of *giving an alternative*: the case of fetal surgery

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**Abstract:** The aim of this paper is to give a contribution to the debate on fetal surgery offering a socio-economic 'reading key' of expected development and future role of prenatal surgical treatment. An overview of the past and present scenario of both performed clinical procedures and applied technologies is presented and the socio-economic factors that, according to our perspective, could strongly influence the dimension and the speed of the innovation process in fetal surgery, both in the clinical and the technological areas, are described. Two specific technological research trajectories in the field of fetal surgery are presented as a contribution to the definition of future development of the technology for prenatal surgical treatment, and a roadmap of the future of fetal surgery is sketched.

**Keywords:** abortion; fetal surgery; healthcare technology; pulmonary athresia; socio-economic perspective; spina bifida; technological roadmap.

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## 1 Introduction

Fetal surgery is a fascinating field to be investigated because, even with a history of more than 20 years, it still represents a challenging research topic with reference both to clinical and technological developments. Furthermore it raises unique and still controversial ethical issues.

The aim of this paper is to contribute to the debate on fetal surgery by offering a more socio-economic 'reading key' of its expected development and future role.

In the next section of the paper – with no claims of exhaustiveness from either the clinical or the technological perspective – the broad picture of the issue addressed is presented[1]. Our aim is to give an overview of the evolutionary track and current state of both performed clinical procedures and applied technologies in fetal surgery.

The third section describes the socio-economic factors that, in our opinion, could strongly influence the dimension and the speed of the innovation process in fetal surgery, in both the clinical and the technological areas.

Two specific technological research trajectories in the field of fetal surgery are introduced in the fourth section as a contribution to the definition of future development of the technology for prenatal surgical treatment. A road map of the future of fetal surgery is sketched in the fifth section, and a paragraph of conclusions closes the paper.

## 2 Fetal surgery: an overview of the clinical and technological aspects

The beginning and the evolutionary pathway of fetal surgery has been strongly stimulated and influenced by advances in technological areas[2] and by the applications to the clinical practice of progresses achieved in several fields of scientific knowledge. The first fetal surgery intervention was performed in 1981 by Harrison at University of California, San Francisco Fetal Treatment Centre, for an open intervention on fetal urinary obstruction.

Fetal surgery is still intended for a restricted number of malformations that cannot be successfully or efficaciously treated after birth. However, since 1981 many life-threatening fetal pathologies have been treated through in utero surgical corrections, approaching prenatal intervention as a valid alternative to neonatal therapy or induced abortion. Starting from the two main American centres that have been performing fetal surgery for more than 20 years – the University of California San Francisco Fetal Treatment Center and the Children's Hospital of Philadelphia, Center for Fetal Diagnosis and Treatment – nowadays about a dozen worldwide centres provide prenatal surgical intervention (Cortes and Farmer, 2004) and many others carry on research and experimentations for specific fetal surgical applications.

In order to frame the process of selection of fetal pathologies to be considered eligible for prenatal surgery under well defined requirements, the International Fetal Medicine and Surgery Society (IFMSS) defined in 1991 some fundamental criteria, which should be met by congenital malformations before being considered for a fetal surgical treatment (Table 1).

**Table 1** Criteria for intrauterine surgery

| | |
|---|---|
| 1 | Accurate diagnosis and staging possible, with exclusion of associated anomalies. |
| 2 | Natural history of the disease is documented and prognosis established. |
| 3 | Currently no effective or too late postnatal therapy. |
| 4 | In utero surgery has been proven feasible in animal models, reversing deleterious effects of the condition. |
| 5 | Interventions are done in specialised multidisciplinary foetal treatment centres within strict protocols, after information of the mother and full consent of the couple. |

*Source:* Papadopulos et al. (2005), adapted from Harrison (1991).

Fetal surgical interventions for the treatment of the following pathologies were successfully experimented more than ten years ago (Adzick and Harrison, 1994).

- Congenital Cystic Adenomatoid Malformation (CCAM): a malformation resulting in an adenomatous overgrowth of the terminal respiratory bronchioles – with associated cysts of variable sizes – and consequent diminution of alveolar growth. Incidence of CCAM has been estimated from 1 in 25,000 to 35,000 pregnancies (in Canada) (Laberge et al., 2001; Cortes and Farmer, 2004).

- Congenital Diaphragmatic Hernia (CDH): a defect that occurs when the fetal diaphragm does not fully form, allowing for abdominal visceral herniation with subsequent pulmonary hypoplasia (arrested development of the lungs). It occurs with an incidence of one in 2,400 live births per year in the US (Langham et al., 1996).
- Urinary Tract Obstruction (UTO): it is included in fetal urinary tract abnormalities comprising up to 50% of prenatally diagnosed malformations – as noted in a retrospective review of 12,000 patients (Cortes and Farmer, 2004; Helin and Persson, 1986). Posterior urethral valves account for the most common cause of male urinary tract obstruction with an incidence reported of one in 8,000–25,000 live births (Cortes and Farmer, 2004; Dinneen and Duffy, 1996).
- Sacrococcygeal Teratomas (SCT): a rare subset of germ cell neoplasms; frequently located in the sacral area, these tumours are closely adherent to the coccyx. Incidence is reported as 1 in 35,000 live births, and they are considered the most common tumour in the newborn (with a 4:1 female preponderance) (Cortes and Farmer, 2004; Grosfeld and Billmire, 1985; Holzgreve et al., 1987).
- Twin-Twin Transfusion Syndrome (TTTS): it is the result of an imbalance in net blood flow between monozygotic twins – that have a placental vascular communication – bringing in most cases to hydramnios of the recipient twin with high risk of perinatal death and cerebral palsy in survivors. It occurs in approximately 15% of monozygotic twin pregnancy; the latter occurs with an incidence of 3.5 per 1000 births (Ville et al., 1995).

The use of fetal surgery has been gradually expanded to the treatment of many other fetal pathologies or malformations, even to the not lethal ones. An example is myelomelingocele, better known as 'spina bifida', a congenital defect of the central nervous system with severe morbidity and significant mortality and a birth prevalence of 4.6 cases per 10,000 births (Lary and Edmonds, 1996; Walsha and Adzick, 2003; Cortes and Farmer, 2004). Fetal surgical treatment is now being attempted for intrauterine correction of cleft lip and palate (Papadopulos et al., 2005) up to the recent experimentation of in utero treatment of metabolic cellular defects, such as stem cell/enzyme defects and predictable organ – heart, kidney, lung – failure (Harrison, 2003).

Progress in fetal surgery refers not only to the extension of its use to some more, well defined, pathologies, but also to innovation in techniques and instruments which can be used to perform the intervention.

One of most recent and innovative trends in fetal therapy is definitely the use of minimally invasive techniques, intended as an alternative to open – through hysterotomy – surgery. These procedures are performed through the use of small trocars and a combination of videofetoscopic and sonographic visualisation (Harrison, 2003).

Fetoscopy was not entirely unknown in fetal therapy: it has been used in the 1980s for fetal blood sampling and afterwards replaced, for this specific diagnostic application, by the ultrasound technology (Gratacos and Deprest, 2000).

Subsequent progress in the endoscopic technology, together with a wider understanding and insight into the patophysiology and the improvements towards the definition of anaesthetic and tocolytic strategies, brought, in the late 1990s, about ten years later the first minimally invasive performed procedure[3], to the re-introduction of fetoscopy for prenatal surgical treatment of fetal malformations (Gratacos and Deprest, 2000).

The progressive reduction in diameter of endoscopes and the improvement in the performance of micro-instrumentation allowed the introduction, and contributed to the diffusion, of fetal endoscopic surgery.

Fetoscopic surgery is performed through the placement of 9–15 French radially expanding trocars that allow the positioning of endoscopes (from 3 to 15 French), irrigation tubing or fetoscopic instruments. It can be done either through the mother's skin (percutaneous) or, in some circumstances, it requires a small opening in the mother's abdomen (mini-laparotomy) (Cortes and Farmer, 2004).

The first fetal endoscopic procedures were performed in the 1990s for the correction of diaphragmatic hernia (Harrison et al., 1998) and for coverage of myelomeningocele (Bruner et al., 1999).

Other fetoscopic interventions, for the correction of a twin–twin transfusion syndrome, were performed in 1995, using a rigid fetoscope (6 French in diameter), housed in a 8 French cannula under anaesthesia and continuous ultrasound visualisation (Ville et al., 1995) and for a fetal SCT, and in 1996, using a 6 French diameter rigid fetoscope with a field of vision of 60° introduced percutaneously into the amniotic cavity through a sheath of 9.8 Charriere under local anaesthesia and maternal analgesia (Hecher and Hackeloer, 1996).

At present, the pathologies that are treated by endoscopic fetal surgery are (Gratacos and Deprest, 2000):

- Congenital Diaphragmatic Hernia (CDH): the endoscopic approach was first attempted by the University of California San Francisco group (Harrison et al., 1998) with a 69% (11/16) survival (Albanese et al., 2000).
- Myelomeningocele: the fetoscopic approach has been tried (Bruner et al., 1999) and abandoned due to technical complexity and poor outcomes (Gratacos and Deprest, 2000).
- Lower Urinary Tract Obstruction (LUTO): the first intervention was reported in 1995 and the technique is currently performed by several centres (Gratacos and Deprest, 2000).
- Sacrococcygeal Teratoma (SCT): there is also one report on successful fetoscopic laser coagulation of the feeding vessels, (Hecher and Hackelor, 1996) even if the definitive intervention is still postponed after the birth (Gratacos and Deprest, 2000).
- Twin-Twin Transfusion Syndrome (TTTS): standard therapy for this malformation, at present, varies (amnioreduction or intertwin membrane septostomy or fetoscopy); fetoscopic applications essentially refer to ablation of intertwin vascular connections (Cortes and Farmer, 2004).

Whether the endoscopic approach is the best approach for some fetal operations is still under debate. The rationale of fetoscopic surgery, as for minimally invasive surgery in general, is to achieve the minimisation of both invasiveness and complications of surgical treatment and, in particular for fetal endoscopic treatment, enabling to keep the fetus in its natural environment.

In open fetal surgery, the pregnant woman is anaesthetised and an incision, long enough to allow uterus exposure, is made in her abdomen. Then the uterus is cut and opened and surgical intervention on the fetus is performed.

The large hysterotomy site increases morbidity due to the disruption of fetal membranes at the time of the intervention and produces considerable exposure to infections. Longer hospitalisation is required together with cesarean delivery of present and future pregnancies. Preterm labour and preterm delivery often occur. Preterm labour, which has been described as the 'Achilles' heel' of fetal surgery, may strongly benefit from minimally invasive approaches (Lierly et al., 2001; Flake, 2003).

Michael Harrison, one of the pioneers of fetal surgery, while listing the important results nowadays achieved in the field of fetal surgery (Harrison, 2003) – the fetus is a patient, the fetal patient has a doctor/surgeon, fetal surgery has its own society (the Fetal Medicine and Surgery Society), its own journal (*Fetal Diagnosis and Therapy*) and successful textbook (e.g. 'The Unborn Patient: The Art and Science of Fetal Therapy'), the number and quality of (fetal) surgical professional increase and the number of centres is growing – states the success of this kind of surgery. But some lines above in the same paper he draws the attention to several open issues in performing fetal surgery, referring principally to technical problems and, in particular, to the need of more appropriate instruments to be developed in order to better perform fetal endoscopic surgery.

Also Flake (2003) assumed that the future development of fetal surgery should pass through the overcoming of the two main current limitations: biological constraint – intrinsic to fetal conditions- and technological unsolved problems.

Specific devices for fetal endoscopic surgery, small trocars and dissecting instruments, need to be studied, designed and developed addressing specifically fetal surgery procedures. Possible answers to still open issues on fetal surgery could come, according to Flake, from the improvements in the imaging technology and the possible applications of robotics to fetal therapy.

## 3 A different 'reading key' of the progress in fetal surgery

The previous overview of the literature about fetal therapy helped us in drawing a sketch of some of the most relevant characteristics of the past and present scenarios in fetal surgery.

The intense debate involving this important surgical field, its applications and its future development must be underlined. Issues on fetal surgery are matter of discussion in an 'enlarged' scientific community, formed by medical specialists – surgeons, obstetricians, perinatologists, geneticists, pediatricians, neurologists, sonologists, neonatologists, anesthesiologists, gynaecologists – together with physiologists, biologists, tissue engineers, bioengineers and bioethicists.

As pointed out in the previous section, the field of fetal surgery is still open to wide improvements in the clinical practice and in enabling technologies. Bioethical aspects represent a part of an important, sometimes harsh, debate about ethical implications of fetal surgery that has gone along with its development since from the very beginning.

Bioethics, in fact, is a fundamental issue in fetal therapy since this procedure involves the interests of both the fetus and the mother, and they may conflict.

Unique and rather unsolved questions are raised: who is *the* patient, the fetus or the mother? If *the* patient is the fetus, does it mean that the fetus has an independent moral status (Chervenack and McCullough, 2002; Chervenack, McCullough and Birnbach, 2004)? When and whether the fetus is a person (Howe, 2003)? Are the risks resulting from a fetal surgical intervention acceptable? Who should decide (Howe, 2003)? On this regard the bioethics literature is very rich and different philosophic approaches are proposed.

Other ethical questions that have been raised refer to the impact of using innovative procedures and technologies (Lierly et al., 2001; Elam-Evans et al., 2003).

Recently the bioethicists are focusing on the effects of the expansion of the use of prenatal surgery for non-lethal fetal pathologies treatment – such as the correction of myelomeningocele or cleft lip and palate repair. In this case the procedure doesn't aim to avoid death of the fetus, but to improve quality of life after birth (Howe, 2003).

We wish to join herein the debate about fetal surgery by proposing also a more socio-economic 'reading key'. Our point is that the socio-economic perspective could represent a relevant factor influencing the innovation process in fetal surgical therapy.

From a socio-economic point of view, fetal surgery may represent a possible, and in most cases unique, alternative to women (or couples) who consider 'elective' therapeutic abortion unacceptable because it is a 'costly' option, where costs are mainly intended in the meaning of social, psychological, intangible ones.

If the case-fatality rate of abortion has been gradually decreasing and, leaving out the cases of *unsafe abortion*, the risk of complications is not higher than for most medical and surgical treatment. If direct and indirect costs of abortion may be considered not so significant, we should not underestimate the intangible social costs deriving to the society from psychological long-term effect of abortion. In particular it can not be ignored how costly may be the condition of having no alternative for women (or couples) who would have not chosen abortion.

We are strongly convinced that offering an alternative to abortion (in most cases the only solution offered today), and this is the future we envisage for fetal surgery, has an important significance for the patient today and more and more for healthcare procedures in the future.

To give an alternative is a task that falls within the duties of science and research, in respect of universally agreed bioethical principles. This would increase people's freedom of choice, and this is always (especially in healthcare) an important value, a great achievement for the whole society.

In our opinion, the dimension and the speed of innovation in fetal surgery is strongly dependent on the importance that we decide to give to having an alternative. This condition is common in other similar areas where the number of patients is not high, the innovation process is expensive, the standard solution is easily available and the indirect and intangible costs are mainly not covered by the healthcare system.

## *3.1 The price of abortion*

Abortion, as almost every surgical treatment, is not free from risk of complications, even if rarely lethal.

From a survey carried out in USA in 2000 (Elam-Evans et al., 2003) by the Centre for Disease Control and Prevention (CDCP), it resulted that the annual number of deaths associated with known legal induced abortion in 1990s decreased by approximately 70% if compared with 1972. In 1972, 24 women died from causes associated with legal abortions and 39 died as a result of known illegal abortions. In 1999, four died as a result of legal induced abortion and none died as a result of illegal induced abortion (Table 2).

**Table 2** Number of deaths and case-fatality rates* for abortion-related deaths, by type of abortion – US, 1972–1999 (per 3 years)

| | *Type of abortion* | | | | |
|---|---|---|---|---|---|
| | *Induced* | | | | |
| *Year* | *Legal* | *Illegal* | *Unknown*† | *Total* | *Case-fatality rate** |
| 1972 | 24 | 39 | 2 | 65 | 4.01 |
| 1975 | 29 | 4 | 1 | 34 | 3.04 |
| 1978 | 9 | 7 | 0 | 16 | 0.08 |
| 1981 | 8 | 1 | 0 | 9 | 0.6 |
| 1984 | 12 | 0 | 0 | 12 | 0.9 |
| 1987 | 7 | 2 | 0 | 9 | 0.5 |
| 1990 | 9 | 0 | 0 | 9 | 0.6 |
| 1993 | 6 | 1 | 2 | 9 | 0.5 |
| 1996 | 9 | 0 | 0 | 9 | 0.7 |
| 1999 | 4 | 0 | 0 | 4 | X |
| Total | 351 | 93 | 15 | 459 | 1.1** |

*Legal induced abortion-related death per 100,000 reported legal induced abortion.

**Case-fatality rate computed for 1972-1997 only.

†Unknown whether abortion induced or spontaneous.

x Case-fatality rates for 1998–1999 cannot be calculated because a substantial number of abortion occured in nonreporting states.

*Source:* Elam–Evans et al., 2000.

According to the data released by the CDC (Elam-Evans et al., 2003), the risk of dying as a direct result of a legally induced abortion is less than one per 100,000. This risk increases with the length of pregnancy:

- One death for every 530,000 abortions at 8 or fewer weeks
- One death per 17,000 at 16–20 weeks
- One death per 6,000 at 21 or more weeks.

Apart from 'unsafe abortion', which WHO defines as "a procedure for terminating an unwanted pregnancy either by persons lacking the necessary skills or in an environment lacking the minimal medical standards or both" (Ahman and Shah, 2002) affecting mostly developing countries, the clinical procedure itself presents risks of several complications, as every medical/surgical intervention. Complication rate doubles with each 2 weeks delay after 8 weeks of gestation and it increases with the advancing of the gestational age.

The risks of possible complications also depend on the abortion procedure:

- non-surgical-pharmacological-abortion
- vacuum aspiration abortion

- dilation and curettage abortion
- dilatation and evacuation
- labour induction
- hysterotomy (similar to a cesarean section).

Possible complications may range from allergic reaction to the medications, painful cramping, nausea and/or vomiting for the pharmacological treatments to pelvic infection, heavy bleeding, torn cervix, perforated uterus, severe infection (sepsis), injury to the urinary tract for the more invasive procedures, leaving out anesthesia-related complications.

Long-term risks of abortion also need to be considered. The connection of induced abortion with increased risk of breast cancer is not universally acknowledged, as supposed in some studies. Two reports presented in the US by the National Cancer Institute in 2003, and by a cancer research group from Oxford University in 2004, concluded that there is no clear evidence of a causal relationship between abortion and breast cancer.

From a review of observational studies on long-term consequences of induced abortion carried out at the Department of Epidemiology, School of Public Health, University of North Carolina, it resulted that the induced abortion is not associated with risks about future childbearing, spontaneous abortion and ectopic pregnancy. However it increases the risk for subsequent pre-term termination of pregnancy and depression (Thorp, Hartmann and Shadigian, 2003).

Consequences of induced abortion have been investigated even from a psychiatric perspective. At the Department of Psychiatry, Queen's Medical Centre, Nottingham, 67 women were interviewed 4 weeks after spontaneous abortion: 32 of these women resulted as psychiatric cases. This result is four times higher than in the general population of women. In each case the diagnosis was depressive disorder: this finding confirmed by the scores obtained after administering three different depression rating scales (Friedman and Gath, 1989).

The psychological effect of a pregnancy termination is particularly significant if the cause of abortion is a fetal abnormality. From a cross-sectional study performed in 254 women, 2–7 years after termination of pregnancy for fetal anomaly at Division of Perinatology and Gynaecology of the University Medical Center Utrecht, resulted that 17.3% of the participants showed pathological scores for posttraumatic stress (Ashton, 1980). Higher levels of long-term psychological morbidity were associated with advanced gestational age, low perceived support from partner and low educational level (O'Brien, 1984).

Higher negative emotional effects were noticed in the case of abortion due to a fetal anomaly that was presumably compatible with life (Korenromp et al., 2005).

The scientific debate is recently raising concerning the hypothesis to include in the informed consent, required before induced abortion, information about the risk of abortion, in particular the risk of subsequent preterm delivery and depression (Thorp, Hartmann and Shadigian, 2003).

The negative socio-economic impact of induced abortion is proved and, in the case of fetal malformation, it results as highly negative.

From a more rigorous economic point of view and according to the Cost of Illness approach, the social costs of elective abortion go beyond the direct ones, related to the resources employed in delivering the medical treatment and depend on the selected abortion procedure – plus costs for the treatment of complications, if any. Direct costs of abortion can be reckoned in in-patient and day case admissions, out-patient consultations, general practitioner consultations and numbers of prescriptions (Thomas and Morris, 2003). Costs of abortion go even further indirect ones, essentially related to the lack of productivity (inability to work) of women, due to their condition (morbidity costs) and to the assistance required. High intangible costs associated with psychological long-term consequences of induced abortion affect the social welfare.

For the above mentioned reasons, we believe that alternative technical solutions to induced abortion for fetal pathologies are worthy to be deeply investigated.

### *3.2 The numbers of abortion*

Fetal surgery may represent a future alternative to therapeutic abortion which is nowadays performed:

1 to terminate a pregnancy that would result in the birth of a unhealthy child

2 to terminate a nonviable pregnancy

3 to selectively reduce a multifetal pregnancy.

From this perspective, the incidence of pathologies that could be treated through fetal surgery, according to some published data, is expected to increase till to a maximum of 35 per 1000 women aged 15–44 or 26 per 100 known pregnancies, that are some estimated abortion rate and ratio[4] (Henshaw et al., 1999) (Table 3).

For the topic we address, from the abortion rate or ratio presented in Table 3, data relative to abortions performed because of unintentional pregnancies and maternal diseases, have to be subtracted. Some studies point out that approximately 3–5% of all newborns have a recognisable birth defect (Roche, 2004).

More complete surveys have to be carried out in order to have a more precise assessment of the number of cases that could benefit from the alternative of fetal surgery.

The data about costs and number of abortion presented in this section only aim to give a glimpse on the overall dimension of the phenomenon and, ultimately, on the alternative solution proposed to it.

Costs and numbers of abortion call for seriously investigating an alternative to therapeutic abortion.

## 4 Promising research trajectories on fetal surgery

The possibility of the implementation of the alternative to therapeutic abortion, that is the future role of fetal surgery, passes through technological innovation.

An emerging research trajectory that could strongly contribute to improvement of prenatal surgical treatments is worthy to be mentioned.

The research is deeply focused on some peculiar pathologies: pulmonary athresia and spina bifida or myelomeningocele.

The former is a congenital cardiac malformation, which is not efficaciously treatable after birth. Up to now, fetal surgery for the treatment of pulmonary athresia was experimented just on animals. It is still highly invasive as an open procedure is required.

Results till now achieved through experimentation seem not to encourage the application of open surgery to human fetus.

The proposed research trajectory aims to enable a minimally invasive fetal surgery for the treatment of pulmonary athresia. The main objectives of the research is to develop a micro-catheter integrating a tissue palpation device to perform incisions on selected area of the heart-vessels system. The sensing device is based on a micro-resonator which is able to detect the stiffness of the heart tissue, thus giving clear indication of the area to be cut. Moreover, the micro-catheter should include an impedance sensor to give additional information on the tissue quality.

**Table 3** Estimated number of induced abortions, by legal status, percentage of all abortions that are illegal, abortion rate and abortion ratio, all according to region and subregion – 1995

| *Region and subregion* | *No. of abortions (millions)* | | | *% illegal* | *Rate** | *Ratio†* |
|---|---|---|---|---|---|---|
| | *Total* | *Legal* | *Illegal* | | | |
| Total | 45.5 | 25.6 | 19.9 | 44 | 35 | 26 |
| Developed regions | 10.0 | 9.1 | 0.9 | 9 | 39 | 42 |
| Excluding Eastern Europe | 3.8 | 3.7 | 0.1 | 3 | 20 | 26 |
| Developing regions | 35.5 | 16.5 | 19.0 | 54 | 34 | 23 |
| Excluding China | 24.9 | 5.9 | 19.0 | 76 | 33 | 20 |
| Africa | 5.0 | ‡ | 5.0 | 99 | 33 | 15 |
| Asia | 26.8 | 16.9 | 9.9 | 37 | 33 | 25 |
| Europe | 7.7 | 6.8 | 0.9 | 12 | 48 | 48 |
| Latin America | 4.2 | 0.2 | 4.0 | 95 | 37 | 27 |
| Northern America | 1.5 | 1.5 | ‡ | – | 22 | 26 |
| Oceania | 0.1 | 0.1 | ‡ | 22 | 21 | 20 |

*Abortions per 1,000 women aged 15–44.

†Abortions per 100 known pregnancies (Known pregnancies are defined as abortions plus live births).

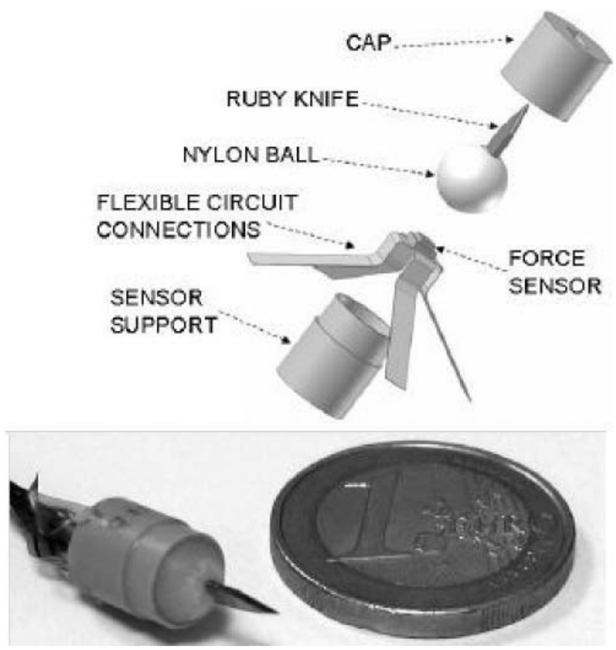
‡fewer than 50,000

*Notes:* Developed regions include Europe, Northern America, Australia, New Zealand and Japan; all others are considered developing. Regions are as defined by the United Nations (UN).

*Sources*: Populations--UN, The Sex and Age Distribution of the World Population, The 1996 Revision, New York: UN, 1997. Births--UN, World Population Prospects: The 1996 Revision, Annex II & III, Demographic indicators by major area, region and country, New York: UN, 1996. Illegal abortions-- WHO, 1998.

Spina bifida, one of the most common fetal diseases, consists of an incomplete closure in the spinal column. A new surgical robotic system for intrauterine fetal surgery in an Open MRI has been proposed by Harada et al. (2005). In the proposed surgical procedure, the abdominal and uterine wall would not widely be opened but rather surgical instruments would be inserted through the small holes in both walls to perform minimally invasive surgery. A prototype of the micro-manipulator of diameter is 2.4 mm and bending radius 2.45 mm has been developed for this purpose. The diameter and bending radius of this manipulator is one of the smallest ever developed among surgical robots. The mechanism of the manipulator includes two ball joints and is driven using four wires able to bend through 90° in any direction. On the distal end of such a tool, a knife for sharp cutting of the abdominal and uterine tissues has been included. Two main issues have to be considered during the cutting procedure: the first one is that abdominal and uterine walls must be penetrated at the same time in order not to damage uterine inner membranes, while the second is that a strong pushing force could result in paralytic lower limbs. For these reasons a Micro-Electric-Mechanical-System (MEMS) triaxial force sensor, described in Beccai et al. (2005) and Valdastri et al. (2005), has been included on the tip of the surgical instrument, and mechanically connected to the blade (Valdastri et al., 2006) (Figure 1).

**Figure 1** The surgical instrument developed at Scuola Superiore Sant'Anna




This enables a precise sensing of the force applied from the knife to the tissues and a measurement of its direction. Thus a sharp cutting can be achieved by applying a piezoelectrical actuation when the blade is touching the skin in a perpendicular orientation. The design of this surgical microtool represented in Figure 1 has been carried on by using Magnetic Resonance Imaging (MRI) safe and compatible materials, in order to take advantage from Open MRI imaging during the surgical procedure. This would enable a more precise localisation of the fetus and the target location if compared to other standard imaging methods, like ultrasonography.

The proposed techniques can be generalised to other areas of surgery where a triaxial force feedback is required or, at least, can improve the standard practice. Some examples are proposed.

- Minimally Invasive Robotic Surgery (MIRS): thanks to triaxial force sensing, the surgeon can drive the robotic manipulator during MIRS operations taking advantage of real time force feedback, thus avoiding unwanted damages to the tissues. Clinical applications addressed through MIRS are all types of surgical procedures that can be performed through 1–2 cm incisions or operating ‘ports’ (e.g. urologic, gynaecologic, thoracoscopic, etc.).
- Oftalmic surgery: all pathologies of retina, now treated through vitrectomy (diabetic vitreous hemorrhage, retinal detachment epiretinal membrane, macular hole, proliferative vitreoretinopathy, endophthalmitis, intraocular foreign body removal, etc.) could be better addressed thanks to the high force resolution of the force sensorised system that can be reduced, with further technological improvements, down to 50 μN.
- Endoluminal surgery: this field can be addressed thanks to the small dimensions that could be obtained with a further miniaturisation of the proposed device, i.e. an outer diameter of 2.95 mm can be easily obtained for the force sensing device, thus enabling its insertion through a nine French catheter guide.
- Catheter insertion: usually medical doctors insert catheters by turning and selecting manually the right branch to explore, without any feedback from sensorised systems; this procedure requires a long training and high skills. Embedding a triaxial force sensing system on the tip of a catheter could give a quantitative measure of the pushing force and damage to the lumen walls can be avoided.

## 5 The proposed roadmap for fetal surgery

The future role of fetal surgery, according to the ‘reading key’ so far proposed and described in the previous sections of this paper, is to represent an alternative to abortion. Fetal surgery could offer an effective surgical therapy to the clinical cases now treated through the therapeutic termination of pregnancy.

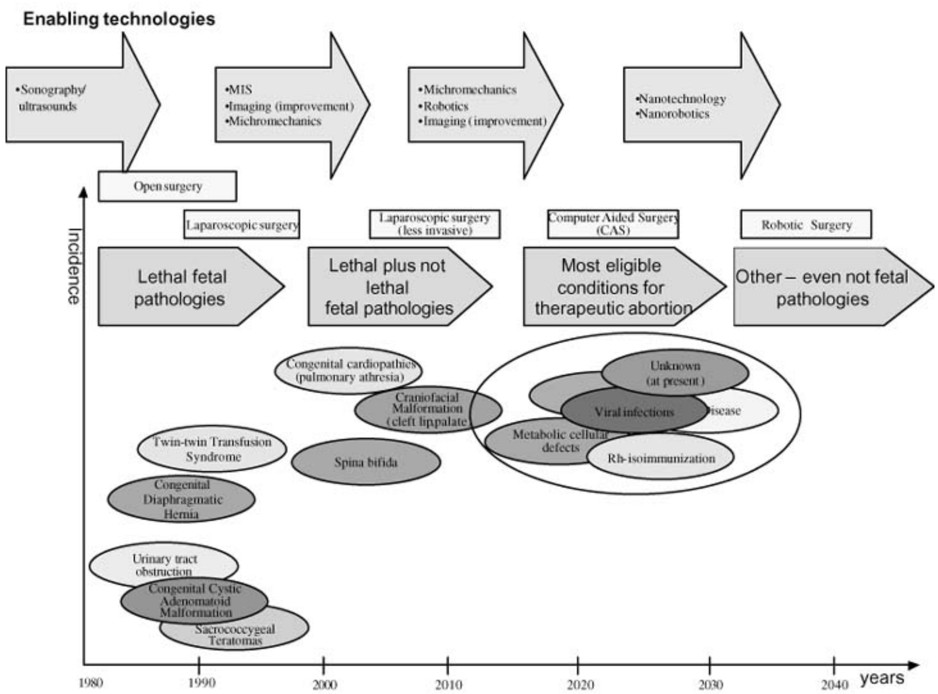
Many clinical and technological open questions need to be solved in order to reach this goal (Figure 2).

The progress in the sonographic technology, which allows an accurate diagnosis of fetal anomalies, gave a strong stimulus to the beginning of fetal surgery more than twenty years ago.

About ten years later, improvements in imaging technology and in minaturisation of surgical instruments, enabled the use of minimally invasive surgery for fetal therapy.

The future steps in order to enhance the field of application of fetal surgery go through the development of instruments *specifically* addressing fetal surgery procedures. Till now *standard* clips, balloons, trocars and other surgical tools are used in fetal surgical treatments. This is a limit that prevents further extensions of fetal surgery and increases the risks of the procedures performed. At present, the incidence and the complications associated with minimal fetoscopic procedure are equivalent to those resulting from open fetal treatment.

**Figure 2** A roadmap of fetal surgery




*Source*: Our elaboration

Further improvement in imaging, in micromechanics and applications of robotics would strongly contribute, in the next years, to a wide progress in fetal surgery. Nanotechnology and molecular robotics will definitely change the scenario of fetal surgery in next decades. They will allow the overcoming of the unsolved problems now limiting the application and the extension of fetal surgery:

- lack of specific instrumentation
- invasiveness of the procedure
- limited and unsatisfactory movements of the surgeon.

## 6 Conclusions

This paper proposes a socio-economic 'reading key' to the innovation process in clinical-technological areas enabling fetal surgery.

The aim is to contribute to further enlarge the scientific debate about prenatal surgical treatments and to provide further factors influencing the definition of the technological roadmap of fetal surgery.

Further steps have to be taken forward in economic analysis in this surgical procedure. The future goal is to measure and compare the costs and the benefits associated with the two alternative solutions, abortion and fetal surgery. Data have to be collected and analysed. In particular, intangible and social costs and benefits of the two choices cannot to be ignored.

Moreover, in this socio-economic evaluation, it will be necessary to consider not only the benefits for fetuses and mothers (couples), but also the benefits that many other patients affected by different pathologies could derive from potential improvements achieved in fetal surgery. Some possible future applications of the proposed technology in other surgical areas have been identified in this paper.

In other words, in this proposed analysis the following relevant question has also to be addressed: what would be the opportunity costs of *not* pursuing the fetal surgery trajectory, of not giving an alternative?

## References

Adzick, N.S. and Harrison, M.R. (1994) 'Fetal surgical therapy', *The Lancet*, Vol. 343, pp.897–902.

Ahman, E. and Shah, I. (2002) 'Unsafe abortion: worldwide estimates for 2000', *Reproductive Health Matters*, Vol. 10, pp.13–17.

Albanese, C., Chiba, T., Paek, B., Farmer, P., Sandberg, P., Farrell, J., Filly, R. and Harrison, M. (2000) 'Fetal tracheal occlusion for severe left congenital diaphragmatic hernia', *American Journal of Obstetrics and Gynecology*, Vol. 182, p.S182.

Annual Therapeutic Abortion Survey (2002) 'Statistics Canada', Available at: http://www.statcan.ca.

Ashton, Y. (1980) 'The psychosocial outcome of induced abortion', *British Journal of Obstetrics & Gynecology*, Vol. 87, pp.1115–1122.

Beccai, L., Roccella, S., Arena, A., Valvo, F., Valdastri, P., Menciassi, A., Carrozza, M.C. and Dario, P. (2005) 'Design and fabrication of a hybrid silicon three-axial force sensor for biomechanical applications', *Sensors and Actuators A*, Vol. 120, pp.370–382.

Bilton, M.G. (2003) 'Ethics: 'life before birth' and moral complexity in maternal fetal surgery for spina bifida', *Clinics in Perinatology*, Vol. 30, pp.449–450.

Bruner, J.P., Richards, W.O., Tulipan, N.B. and Arney, T.L. (1999) 'Endoscopic coverage of fetal myelomeningocele in utero', *American Journal of Obstetrics and Gynecology*, Vol. 180, pp.153–158.

Chervenack, F.A. and McCullough, L.B. (2002) 'A comprehensive ethical framework for fetal research and its application to fetal surgery for spina bifida', *American Journal of Ostetrics and Gynecology*, Vol. 187, pp.10–14.

Chervenack, F.A., McCullough, L.B. and Birnbach, D.J. (2004) 'Ethical issue in fetal surgery research', *Best Practice & Research Clinical Anaesthesiology*, Vol. 18, pp.221–230.

Cortes, R.A. and Farmer, D.L. (2004) 'Recent advances in fetal surgery', *Seminars in Perinatology*, Vol. 28, pp.199–211.

Dinneen, M.D. and Duffy, P.G. (1996) 'Posterior urethral valves', *British Journal of Urology*, Vol. 78, pp.275–281.

Elam-Evans, L.D., Strauss, L.T., Herndon, J., Parker, W.Y., Bowens, S.V., Zane, S. and Berg, C.J. (2003) 'Abortion surveillance – United States, 2000', in *CDC Surveillance Summaries*, November 28, 52(SS12), pp.1–32.

Flake, A.W. (2003) 'Surgery in the human fetus: the future', *Journal of Physiology*, Vol. 547.1, pp.45–51.

Friedman, T. and Gath, D. (1989) 'The psychiatric consequences of spontaneous abortion', *The British Journal of Psychiatry*, Vol. 155, pp.810–813.

Gratacos, E. and Deprest, J. (2000) 'Current experience with fetoscopy and the Eurofoetus registry for fetoscopic procedures', *European Journal of Obstetrics & Gynecology and Reproductive Biology*, Vol. 92, pp.151–159.

Grosfeld, J.L. and Billmire, D.F. (1985) 'Teratomas in infancy and childhood', *Current Problems in Cancer*, Vol. 9, pp.1–53.

Harada, K., Tsubouchi, K., Fujie, M.G. and Chiba, T. (2005) 'Micro manipulators for intrauterine fetal surgery in an open MRI', Paper presented at the *IEEE International Conference on Robotic and Automation (ICRA'05)*, Barcelona, Spain, pp.504–509. In proceedings.

Harrison, M.R. (2003) 'Fetal surgery: trials, tribulations, and turf', *Journal of Pediatrics Surgery*, Vol. 38, pp.275–282.

Harrison, M.R., Mychaliska, G.B., Albanese, C.T., Jennings, R.W., Farrell, J.A., Hawgood, S., Sandberg, P., Levine, A.H., Lobo, E., and Filly R.A. (1998) 'Correction of congenital diaphragmatic hernia in utero IX: fetuses with poor prognosis (liver herniation and low lung-to-head ratio) can be saved by fetoscopic temporary tracheal occlusion', *Journal of Pediatric Surgery*, Vol. 33, pp.1017–1022.

Hecher, K. and Hackeloer, B.J. (1996) 'Intra-uterine endoscopic laser surgery for fetal sacrococcygeal teratoma', *The Lancet*, Vol. 347, p.470.

Helin, I. and Persson, P.H. (1986) 'Prenatal diagnosis of urinary tract abnormalities by ultrasound', *Pediatrics*, Vol.78, pp.879–883.

Henshaw, S.K., Singh, S. and Haas, T. (1999) 'The incidence of abortion worldwide', *International Family Planning Perspectives*, Vol. 25 (Supplement), pp.S30–S38.

Holzgreve, W., Miny, P., Anderson, R. et al. (1987) 'Experience with 8 cases of prenatally diagnosed sacrococcygeal teratomas', *Fetal Therapy*, Vol. 2, pp.88–94.

Howe, E.G. (2003) 'Ethical issues in fetal surgery', *Seminars in Perinatology*, Vol. 27, pp.446–457. http://www.eurofoetus.org/index.htm

Korenromp, M.J., Christiaens, G.C., van den Bout, J., Mulder, E.J., Hunfeld, J.A., Bilardo, C.M., Offermans, J.P. and Visser, G.H. (2005) 'Long-term psychological consequences of pregnancy termination for fetal abnormality: a cross-sectional study', *Prenatal Diagnosis*, Vol. 25, pp.253–260.

Laberge, J.M., Flageole, H., Pugash, D. et al. (2001) 'Outcome of the prenatally diagnosed congenital cystic adenomatoid lung malformation: a Canadian experience', *Fetal Diagnosis Therapy*, Vol. 16, pp.178–186.

Langham, M.R.J., Kays, D.W., Ledbetter, D.J. et al. (1996) 'Congenital diaphragmatic hernia. Epidemiology and outcome', *Clinics in Perinatology*, Vol. 23, pp.671–688.

Lary, J.M. and Edmonds, L.D. (1996) 'Prevalence of spina bifida at birth–United States, 1983–1990: A comparison of two surveillance systems', *MMWR CDC Surveillance Summary*, Vol. 45, pp.15–26.

Lierly, A.D., Gates, E.A., Cefalo, R.C. et al. (2001) 'Toward the ethical evaluation and use of maternal – fetal surgery', *Obstetrics and Gynecology*, Vol. 98, pp.689–697.

O'Brien, T. (1984) 'Induced abortion: anniversary grief reactions', Paper presented at the *Seventh World Congress of Psychiatry*, F.P.757. In proceedings.

Papadopulos, N.A., Papadopoulos, M.A., Kovacs, L., Zeilhofer, H.F., Henke, J., Boettcher, P. and Biemer, E. (2005) 'Foetal surgery and cleft lip and palate: current status and new perspectives', *British Journal of Plastic Surgery*, Vol. 58, pp.593–607.

Quintero, R.A., Hume, R., Smith, C. et al. (1995) 'Percutaneous fetal cystoscopy and endoscopic fulguration of posterior urethral valves', *American Journal of Obstetrics and Gynecology*, Vol. 172, pp.206–209.

Thomas, C.M. and Morris, S. (2003) 'Cost of depression among adults in England in 2000', *British Journal of Psychiatry*, Vol. 183, pp.514–519.

Thorp, J.M., Hartmann, K.E. and Shadigian, E. (2003) 'Long-term physical and psychological health consequences of induced abortion: review of the evidence', *Obstetrics and Gynecology Survey*, Vol. 58, pp.67–69.

Valdastri, P., Harada, K., Menciassi, A., Beccai, L., Stefanini, C., Fujie, M. and Dario, P. (2006) 'Integration of a Miniaturised Triaxial Force Sensor in a Minimally Invasive Surgical Tool', accepted for publication on IEEE Transaction on Biomedical Engineering on March 18, 2006.

Valdastri, P., Roccella, S., Beccai, L., Cattin, E., Menciassi, A., Carrozza, M.C. and Dario P. (2005) 'Characterization of a novel hybrid silicon three-axial force sensor', *Sensors and Actuators A*, Vol. 123–124C, pp.249–257.

Ville, Y., Hyett, J., Hecher, K. and Nicolaides, K. (1995) 'Preliminary experience with endoscopic laser surgery for severe twin-twin transfusion syndrome', *The New England Journal of Medicine*, Vol. 332, pp.224–227.

Walsha, D.S. and Adzick, N.S. (2003) 'Foetal surgery for spina bifida', *Seminars in Neonatology*, Vol. 8, pp.197–205.

## Notes

[1]We based our survey on papers and abstract published from 1982 up to 2005.

[2]'Fetal therapy is the logical culmination of progress in fetal diagnosis' (Adzick and Harrison, 1994) – the quotation referring to improved fetal sonographic and sampling techniques, in particular.

[3]Erich Muhe, Germany, carried out the first laparoscopic cholecystectomy in 1985 (Litynski and Paolucci, 1998; Lau *et al.*, 1997).

[4]Other sources of information define the ratio of the number of induced abortions as 32.2 per 100 live births in 2000 (Annual Therapeutic Abortion Survey, 2002). The CDC estimates that the national abortion rate decreased from 26 per 1,000 in 1992 to 20 per 1,000 in 1997 (Elam-Evans *et al*., 2003).