Chapter 1

Does Twenty-First-Century Technology Change the Experience of Early Pregnancy and Miscarriage?

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Introduction

Miscarriage occurs in approximately 20 per cent of pregnancies and may cause significant distress to many women and their families (Bardos et al. 2015; Nynas et al. 2015). Of the 250,000 miscarriages diagnosed annually in the United Kingdom (UK), 85 per cent happen in the first trimester of pregnancy and approximately 50,000 require hospital admission (National Institute for Health and Care Excellence [NICE] 2012a). Historically, the care of women with miscarriage has largely involved surgical evacuation under general anaesthetic because of concerns regarding the risk of bleeding and infection due to retained pregnancy tissue (Sagili and Divers 2007). In the UK, however, there has been a recent shift towards using expectant management as the first-line treatment choice, where women wait for a miscarriage to be completed naturally without medical or surgical intervention. This has led to significant cost reductions for the National Health Service (NHS) and an improvement in patient satisfaction rates (NICE 2012b).

Women in the UK can access early pregnancy care through their general practitioners and, in some areas, by directly contacting

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dedicated hospital units. Following recent biomedical developments and service changes, hospital admissions due to miscarriage have reduced significantly over the past decade, and so have serious complications such as sepsis and maternal death (NICE 2012a; Sagili and Divers 2007). Moreover, a patient-centred approach empowers women to make informed choices on management options, thus profoundly impacting patients' views about the way they are treated (Bardos et al. 2015). However, the provision of secondary care in the form of emergency gynaecology services is uneven across the country, with regional allocation of resources impacting significantly on availability – and quality – of specialized care (NICE 2012b).

This chapter provides a biomedical account of miscarriage in the UK and particularly in the NHS. It emphasizes terminology changes in recent decades, common causes of miscarriage, diagnostic and treatment pathways, as well as new developments in the field of early pregnancy which have significantly shaped women's views on miscarriage.

Miscarriage: A Biomedical Perspective

Gestational age of the foetus is measured using the first day of a pregnant woman's last menstrual period, meaning that a pregnancy of six weeks' gestation in fact describes an embryo conceived four weeks previously (Jukic et al. 2013). A normal pregnancy lasts between 37 and 42 completed weeks of gestation, and the term 'early pregnancy' encompasses its first trimester – that is, up to 12 completed weeks. This is a period of rapid embryonic cell division and differentiation during which organ formation is established. At 10 weeks, the fully differentiated conceptus is no longer called an embryo and clinicians use the term 'foetus' instead (Chalmers 1992; Nguyen and Wilcox 2005).

Obstetricians have long struggled to develop a unifying nomenclature for pregnancy loss (Chalmers 1992; Silver et al. 2011). This is, to some extent, the result of research input from a wide range of disciplines such as reproductive biology, sociology and anthropology, which in turn has led to inconsistent terminology (Nguyen and Wilcox 2005; Elliot, this volume). The World Health Organization (WHO) defines miscarriage as the demise of a foetus before 22 weeks or weighing less than 500 grams (g). This is somewhat incongruous, given that only at 23 weeks does the average foetal weight reach 500 g (Silver et al. 2011). In the UK, a cut-off of 24 weeks is

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used instead, and at that point the foetus weighs on average 600 g. This is considered the gestational age of viability – before 24 weeks, the foetus is deemed unable to subsist outside the maternal uterus, even though approximately 20 per cent of babies born at 23 weeks of gestation will survive (Seaton et al. 2013). Any pregnancy loss prior to 24 weeks is therefore considered a miscarriage in the UK – early if it occurs before 12 weeks, and late when it happens after the first trimester. Abortion law in England has also used 24 weeks as a cut off for viability, after which time terminations can only be carried out for very specific medical reasons (Berer 2017). In utero death, also known as stillbirth, refers to infants born from 24 weeks onwards without signs of life. Finally, the term 'neonatal death' is used when an infant is born alive after 24 weeks but dies within 28 completed days of life (Silver et al. 2011).

Birth is labelled 'preterm' when it occurs once viability has been reached, that is, between 24 and 37 weeks (Nguyen and Wilcox 2005). An infant born at or around the limit of viability is much more at risk of developing neonatal complications (e.g. infection, respiratory distress and neonatal death) and lifelong disability (e.g. cerebral palsy) than one born after 37 weeks (Seaton et al. 2013). After 37 weeks, a pregnancy is considered to be full term. If a baby is not born spontaneously at 41 to 42 weeks, women are offered induction of labour to prevent in utero death associated with post-maturity (Jucik et al. 2013).

Throughout the years, biomedical advances have led to changes in the terminology applied to early pregnancy (with terms like 'biochemical pregnancy' used when women have a positive pregnancy test but a gestational sac is not visualized with ultrasound, for example) and early pregnancy loss (Chalmers 1992). The term 'abortion' first started to be used in the English language in the mid sixteenth century, with roots in the Latin word *aboriri* (to miscarry) (Kuller and Katz 1994). While the words 'miscarriage' and 'abortion' have been applied interchangeably for centuries by the medical community, women who spontaneously miscarry often prefer the former unless they have voluntarily opted for a termination of pregnancy (Moscrop 2013). In 1985, Beard, Mowbray and Pinker wrote to the *Lancet* calling for a clear distinction between a spontaneous and an induced pregnancy loss (Beard, Mowbray and Pinker 1985). This echoed concerns by their own patients at Saint Mary's Hospital in London, who felt offended by the fact that doctors used the word 'abortion' when referring to miscarriage. A stark decline in academic publication titles using 'abortion' to refer

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to early foetal demise ensued in the United Kingdom (Chalmers 1992), even though internationally it is still a widely used term for miscarriage (Elliot, this volume; Moscrop 2013).

Classification

There are many different classifications for early miscarriage, depending on the clinical presentation and extent of tissue loss – threatened, inevitable, missed, incomplete and complete. The differences between these clinical definitions are often nuanced, and they result in large measure from the widespread use of ultrasound to diagnose miscarriage. In a normal pregnancy, the foetal heartbeat can be detected as early as five weeks of gestation using transvaginal ultrasound. In addition, guidance from the National Institute for Clinical Excellence (NICE) establishes that cardiac activity should be expected on ultrasound imaging whenever the embryo measures more than 7 mm (NICE 2012a). At that size, if a sonographer does not visualize a heartbeat on the ultrasound screen, a diagnosis of miscarriage is made. If the woman is not bleeding vaginally, this is referred to as a 'missed miscarriage'. Missed miscarriages are often detected when women present for their 'dating' scan, which is routinely scheduled for when they are 12 weeks pregnant. Commonly, if the pregnancy is considered uneventful and not requiring any medical intervention, this will be the first scan, and such a diagnosis can result in significant upset in women who are asymptomatic and did not anticipate a problem with their pregnancy (Nikcevic, Tunkel and Nicolaides 1998).

'Threatened miscarriage' refers to vaginal bleeding (with or without abdominal pain) when an ultrasound scan has confirmed that a foetal heartbeat is present and no obvious cause can be identified for the bleeding. Furthermore, a miscarriage is deemed inevitable when, upon performing a vaginal examination, a clinician identifies an open cervix, with or without pregnancy tissue protruding through the cervical canal. The term 'incomplete miscarriage' refers to the passage of some pregnancy tissue through an open cervix, but not all of it – if there is retained tissue inside the uterus, the woman will carry on bleeding and may require medical or surgical intervention. Finally, a miscarriage is considered complete when an ultrasound scan reveals no pregnancy tissue remnants in the uterine lining following vaginal bleeding and loss of tissue (Kolte et al. 2014).

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Pathogenesis

Miscarriage is by far the most common complication of pregnancy, with approximately one in five known pregnancies miscarrying (NICE 2012a). One in four women will experience a miscarriage in their lifetime, with most miscarriages (more than 80 per cent) occurring within the first trimester of pregnancy (Benagiano, Farris and Grudzinskas 2010). Fifty per cent of these contain a gestational sac but no embryonic tissue and have been referred to as a 'blighted ovum', though it has recently been suggested that 'anembryonic miscarriage' is a more appropriate term (Kolte et al. 2014). The remaining half – called 'embryonic miscarriages' – are associated with abnormal development of the embryo and adjacent structures such as the placenta.

Chromosomal abnormalities are involved in approximately half of all miscarriages, although they become less prevalent as gestational age advances; at term, only 5 per cent of stillbirths are due to abnormal chromosomes (Kroon et al. 2011). The most common factor underlying chromosomal anomalies leading to miscarriage is the effect of maternal age (Dunson, Colombo and Baird 2002; Kroon et al. 2011). Indeed, increasing female age is by far the largest independent risk factor for early pregnancy loss. This is thought to derive from a phenomenon called 'meiotic nondisjunction' during egg development, whereby the egg receives an abnormal number of chromosomes and goes on to form a non-viable embryo once fertilized (Benagiano, Farris and Grudzinskas 2010). Numerous studies have shown that the risk of miscarriage is significantly higher in women aged thirty-five years or more. After the age of forty, the miscarriage rate rises exponentially: around 30 per cent of pregnancies will miscarry in women aged forty and 60 per cent at age forty-four (De La Rochebrochard and Thonneau 2002; Dunson, Colombo and Baird 2002; Lean et al. 2017).

The impact of paternal age on the incidence of miscarriage has only more recently been analysed. Study participants are often recruited following attendance at fertility clinics, however, where other confounding features (e.g. smoking status, alcohol intake, female factor infertility) make it difficult to identify an independent effect of male age on a couple's fertility (Johnson et al. 2015). Research by De La Rochebrochard and Thonneau (2002) revealed that in couples where the male was aged forty years and older, maternal age began to have a negative effect on miscarriage earlier, from the age of thirty years. More recently, a large systematic review showed

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that male age is associated with an increase in DNA fragmentation and a decrease in semen volume, total sperm count and normal sperm percentage (Johnson et al. 2015). Unsurprisingly, research investigating DNA quality in sperm has in turn revealed that DNA damage contributes significantly to miscarriage rates (Robinson et al. 2012). Despite the evidence indicating that paternal age has an impact upon the reproductive aspirations of a couple, fertility clinics often ignore it as a contributing factor, particularly because studies have failed to accurately quantify its effect on subfertility (Coughlan et al. 2015).

Obesity, quantified as a body mass index (BMI) above 30 kg/m^2, has become an international epidemic over the past thirty years, with significant consequences for miscarriage and fertility rates (Best, Avenell and Bhattacharya 2017). The prevalence of obesity has nearly tripled since 1975, and more than 600 million adults are obese today (World Health Organization 2017). A raised BMI has been linked to delayed conception in women (Gesink Law, Maclehose and Longnecker 2007), particularly in those who have never conceived before (Wise, Plamer and Rosenberg 2013). In 2008, results from a large Dutch study suggested that in women with regular periods, the probability of conception declined linearly by 4 per cent for every BMI point above 29 kg/m^2 (Van der Steeg et al. 2008). Female obesity has been shown to produce a negative impact on reproductive potential through multiple hormone-mediated mechanisms that affect ovulation, oocyte quality, embryo quality and the endometrium's receptiveness to the implanting embryo (Best, Avenell and Bhattacharya 2017; Broughton and Moley 2017; Talmor and Dunphy 2015). Obese women are therefore at a significantly higher risk of early miscarriage when compared to the general population (Boots and Stephenson 2011; Lashen, Fear and Sturdee 2004). The impact of paternal obesity on miscarriage has been less studied, although research has linked it to increased testicular temperature affecting sperm development, increased oestrogen levels and reduced sperm concentration and motility (Best, Avenell and Bhattacharya 2017; Hammiche et al. 2012; Ramlau-Hansen et al. 2007; Sallmen et al. 2006).

Lifestyle choices play a significant role in miscarriage. For example, legal drugs such as alcohol and tobacco, which many women use widely outside of pregnancy, are well known for their teratogenic effect – that is, they contribute to genetic mutations which may result in abnormal foetal growth or delayed mental development (Goodlett, Horn and Zhou 2005). It remains unclear,

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however, whether only heavy use is associated with an increased risk of miscarriage, with a low-level alcohol intake appearing to be relatively innocuous in early pregnancy (Henderson, Gray and Brocklehurst 2007; Skogerbo et al. 2012). Lee, Sutton and Hartley (2016) analysed the role of the media in portraying sensationalized views of alcohol in pregnancy, and concluded that while researchers themselves often report their results in ways that tend to be overly cautionary, the media then tends to introduce and perpetuate factual inaccuracies by highlighting some of those findings and omitting others. Excessive caffeine consumption is significantly associated with a rise in miscarriage risk, and studies suggest that there may be a benefit in reducing caffeine intake to less than 200 mg per day – about two cups of regular coffee (Chen et al. 2016).

Occupational exposure to environmental toxins in a workplace setting has also been reported as potentially contributing to miscarriage – substances like arsenic, lead, formaldehyde and benzene have all been the object of scientific studies (Kumar 2011; Lamadrid-Figueroa et al. 2007; Quansah et al. 2015). Moreover, chemotherapy drugs and X-ray tests have been linked to an increased risk of miscarriage in nurses and technicians who handle them regularly (Lawson et al. 2012).

Finally, medical intervention is occasionally responsible for pregnancy loss, particularly in the context of diagnostic procedures that aim at detecting chromosomal abnormalities such as Down Syndrome. This often involves using fine needles to obtain placental tissue or samples of amniotic fluid through the maternal abdomen, and is associated with a 1 to 2 per cent risk of gestational sac rupture and miscarriage (Ogilvie and Akolekar 2014).

Despite new knowledge on the possible reasons contributing to early pregnancy loss, in most instances the specific cause of a woman's miscarriage remains unknown. This is largely the perspective clinicians take when counselling women being treated for miscarriage in the NHS. Women are given advice on how to maximize their health status for pregnancy (e.g. by taking nutritional supplements or seeking specialist input on any known medical conditions that might affect their pregnancies). However, in the absence of categorical evidence identifying a clear reason for a single miscarriage, doctors are generally reluctant to discuss specific risk factors that may have led to foetal demise in hopes of minimizing feelings of guilt in their patients and reiterating the high likelihood of future successful pregnancies (Nynas et al. 2015).

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Treatment

In the UK, miscarriage has been classically treated by surgical evacuation of pregnancy tissue under general anaesthetic, due to concerns about the potential risks of infection and haemorrhage associated with retained pregnancy tissue (Sagili and Divers 2007). Until the late twentieth century, pregnant women with abdominal pain or vaginal bleeding in early pregnancy were admitted to hospital, in order to undergo ultrasound scans and blood tests to confirm pregnancy viability. Prior to the 1980s when ultrasound became more widely available, decisions as to whether a woman was undergoing a miscarriage or ectopic pregnancy were made on clinical signs and symptoms alone (Kuller and Katz 1994). Furthermore, the decision as to whether to proceed with surgical management was made weighing the risks to the mother of not performing an operation with the possible chances of an ongoing pregnancy if conservative management was pursued. When a presumed diagnosis of miscarriage or ectopic pregnancy was made, women would be added to emergency surgical lists. Such lists were at times haphazard, often resulting in unpredictable delays, which aggravated the distress of patients and their families (Sagili and Divers 2007).

In the early 1990s, Bigrigg and Read were the first to report the impact of an innovative approach based on the development of early pregnancy units (EPUs), where multidisciplinary teams of clinicians and nurses provided women with rapid and supportive care (Bigrigg and Read 1991). Access to blood results and ultrasonography was available in EPUs and women were booked into appointment slots in a dedicated clinic where they were appropriately counselled and hence better able to make informed decisions about available management options. The concept quickly gained popularity as it allowed women to access early pregnancy care in an organized manner, with clear improvements in service provision, patient satisfaction rates and cost-effectiveness. Moreover, complications such as sepsis and death associated with surgical procedures became less common (NICE 2012a).

Depending on the clinical circumstances surrounding a miscarriage, women may now choose from a number of different treatment options (Kim et al. 2017). If a woman presents to hospital with vaginal bleeding in pregnancy and a diagnosis of miscarriage is made, she might opt to await events and let the process of miscarriage conclude spontaneously, which occurs in approximately 60 per cent of miscarriages. This process is referred to as 'expectant'

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or 'conservative' management. Alternatively, drugs that promote uterine contractions may be administered in the form of tablets or vaginal pessaries, in what is commonly referred to as 'medical' management of miscarriage, with a success rate of approximately 80 per cent. Misoprostol is usually the drug of choice for medical management of miscarriage. Following the diagnosis of miscarriage and counselling about treatment options, if a woman opts for medical treatment, a specialist nurse or the patient herself will administer vaginal or oral misoprostol. The woman is then able to return home provided she is in the company of a responsible adult for twenty-four hours. A follow-up telephone consultation usually ensues within the next few days to ensure the woman has passed all of the pregnancy tissue and the bleeding has subsided. If her symptoms are consistent with incomplete miscarriage, the woman will be invited back to the EPU for a repeat ultrasound scan and planning of further management if required. If, however, her bleeding and pain have improved, she will be asked to repeat a urine pregnancy test three weeks later and contact the EPU if the result is positive, as this may indicate retained or invasive placental tissue requiring further specialist input. The third management procedure available to women with miscarriage on the NHS is termed 'surgical' management of miscarriage (SMM), which involves dilatation of the cervix and suction of the pregnancy tissue under local or general anaesthesia. Women may choose this option in the first instance, but SMM is also conducted in situations where conservative and/or medical management fails (Sagili and Divers 2007; Smith et al. 2006).

Several studies have been carried out to compare the outcomes of different treatment options. Meta-analysis data show that on average, women undergoing expectant management are more likely to require an unplanned intervention (e.g. emergency surgery due to first-line treatment failure, surgical completion on maternal request, or treatment to deal with a complication such as infection or bleeding) (Kim et al. 2017). Others have looked at differences in pain severity and duration, although poor methodological quality and high variability resulted in a lack of definitive answers as to which approach is less painful (Wong et al. 2003). Finally, qualitative data on emotional and psychological outcomes and women's satisfaction with management have revealed that many women fear unnecessary intervention, and that there is a general desire for predictability of events and more information from clinicians (Smith et al. 2006).

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While studies comparing different treatment approaches are often of poor quality, a recent systematic review showed that there is no robust medical argument for either of the three options (expectant, medical or surgical) and that the main deciding factor should be the woman's preference (Kim et al. 2017). Moreover, cost analyses have shown that expectant management is significantly less expensive and less taxing on NHS resources (NICE 2012b). Consequently, in the past twenty years there has been a shift towards alternative non-surgical treatment methods which are associated with an equally low (and, in some cases, lower) risk of complications when compared to surgery. However, when a woman presents with severe bleeding or a miscarriage complicated by significant infection, clinicians often advise surgical management as the safest and most effective treatment option (NICE 2012a).

Offering timely and appropriate information to women with miscarriage has a crucial impact on their experience as patients. There is clearly no universal treatment option that suits every individual, but data show that women often have a strong desire to be able to make an informed choice based on full knowledge of the possible outcomes associated with each method (Bardos et al. 2015). In addition, the prospect of clinical treatment as opposed to an expectant approach is often viewed negatively in hindsight, when women wonder whether medical or surgical interventions could have been avoided (Smith et al. 2006). To feel cared for, rather than being an 'object' of care – by both clinicians and their families – is also a key factor in determining women's experiences in the context of miscarriage (Bardos et al. 2015; Smith et al. 2006).

Is Miscarriage a Failure?

The immune system's ability to identify and eliminate foreign organisms, while not causing any damage to tissues recognized by immune cells as 'self', constitutes the basis of defence against external insults such as bacterial infection or mismatched organ transplants (Munoz-Suano, Hamilton and Betz 2011; Pearson 2002). In 1953, Medawar was the first to recognize the immunological paradox of pregnancy: even though half the foetal genes are paternal in origin, rendering it a genetically foreign organism, the maternal immune system tolerates the foetus in successful pregnancy while still being able to avoid infection (Medawar 1953; see also Alecsandru and Garcia-Velasco 2015; Burnet 1959). The

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regulatory mechanisms that allow the successful implantation of a foetus in the uterus are not fully understood. Still, increasing evidence supports a modern paradigm of maternal-foetal tolerance, which postulates that (1) multiple mechanisms provide protection, and (2) both the foetus and the mother contribute to development and maintenance of the pregnant uterus as an immune-privileged site (Hunt et al. 2005; Karsten and Kruse 2008; Pearson 2002; Seavey and Mosmann 2008).

However, the odds of reproductive success are overwhelmingly against the embryo. It is estimated that in humans 70 per cent of embryos will not lead to a healthy live birth: 30 per cent of embryos fail to implant, 30 per cent will miscarry before six weeks of pregnancy and 10 per cent will miscarry at the stage of clinical pregnancy (and before 12 weeks) (Teklenburg et al. 2010). The female body is thought to actively select against embryos that are less likely to develop successfully by imposing natural hurdles that make implantation and ongoing pregnancy more difficult. Evidence suggests that the developmentally competent embryo elicits very little response from cells of the endometrium (that is, the uterine lining) while abnormal embryos provoke an inflammatory response from maternal cells (Chen et al. 2017). Consequently, miscarriage is often viewed by the medical community as a natural process of quality control through which the body recognizes a genetically or developmentally abnormal pregnancy and prevents successful implantation (Benagiano, Farris and Grudzinskas 2010). Given that most human pregnancies are limited to one embryo – and very rarely exceed three – these early barriers are thought to function as a natural selection mechanism through which abnormal progeny are eliminated, thus allowing for further attempts at successful procreation (Chen et al. 2017; Hunt et al. 2005; Karsten and Kruse 2008).

From the moment an oocyte is fertilized and becomes a zygote (that is, the primordial cell that through division will form the human embryo), multiple barriers will hinder the chances of achieving a successful pregnancy. Research has revealed that even in an ideal set of circumstances, the probability of becoming pregnant and achieving a live term birth per menstrual cycle with regular sexual activity is around 20 per cent (Benagiano, Farris and Grudzinskas 2010). A series of unlikely events is required for reproductive success after fertilization. Firstly, the fertilized egg needs to travel from the outer portion of the fallopian tube (where the sperm meets the egg) and reach the endometrium. As it travels through the tube, the embryo will undergo rapid cell division – this alone is prone

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to numerous errors which could trigger cell death and embryonic demise. Upon reaching the endometrium, the embryo will then attach to it through a mechanism called implantation, which occurs on average five to seven days after ovulation. Implantation relies on the development of new blood vessels ('angiogenesis') in a process regulated by local immune cells that render the endometrium tolerant to the formation of a maternal-embryo interface. It is through these developing blood vessels that the embryo will receive sustenance in the form of oxygen and nutrients. Abnormal angiogenesis may therefore halt embryonic attachment and result in reproductive demise (Chen et al. 2017). In fact, implantation anomalies are involved in a myriad of pregnancy complications even when the worst scenario of miscarriage is avoided – these include hypertensive disorders such as maternal pre-eclampsia (a systemic condition marked by high blood pressure and abnormal amounts of protein in a pregnant woman's urine) and impaired growth in the foetus due to a lack of adequate nourishment in utero (Sargent, Borzychowski and Redman 2007).

While the medical community views miscarriage as a normal – and arguably desirable – process that is intrinsically related to natural selection (Coulam 2016), societal interpretations of miscarriage differ dramatically. In recent decades, the age at which women fall pregnant for the first time in mid- to high-income countries has shifted upwards, and the average age for first-time mothers to conceive in England and Wales is currently above thirty years as compared to twenty-six in the 1970s (Lean et al. 2017; Office for National Statistics [ONS] 2016, 2017). Interestingly, in 2015, women aged forty and over had a higher fertility rate than those below twenty years for the second time since 1947 (ONS 2017). This illustrates the overall increase in maternal age as a consequence of women having more control over their reproductive choices, but it is also proof of the technical advances made in the field of assisted reproduction over the past couple of decades. At the age of forty, a woman who has not been able to conceive despite trying naturally will still have a live birth rate of approximately 50 per cent if she opts to undergo in vitro fertilization (IVF) using a donor egg (Yeh et al. 2014).

As mentioned above, older age comes with an inevitable decline in fertility. It is therefore understandable that, among a plethora of environmental stressors and delayed fulfilment of fertility aspirations, higher stakes are involved when couples do decide to actively try to fall pregnant. Women commonly engage in pre-conception

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planning which may entail medical check-ups, lifestyle changes (like smoking or alcohol cessation) and nutritional supplementation with folic acid, which is known to decrease the risk of neurological abnormalities in the foetus (Lindqvist et al. 2017; Pitkin 2007). Technological developments that aid in tracking one's menstrual cycle have now become widespread, with online tools and apps trying to predict a woman's optimal fertile period. Women have access to personal kits that measure urinary levels of luteinizing hormone at the time of ovulation, which is used to predict the optimal time to have sexual intercourse and increase the chances of becoming pregnant. Research has yet to validate the value of such tests and their impact on conception rates, but regardless, they are now commonplace among those trying to conceive (Su et al. 2017).

When such high personal effort is put into conceiving, it is unsurprising that miscarrying a wanted pregnancy should bring feelings of disappointment, sadness and – at times – guilt (Bardos et al. 2015; Wong et al. 2003). Indeed, many women fear their miscarriage might have been a result of something they did wrong – and they worry that their partners and family too would see them as culprits of an event that they may not perceive as unavoidable (Adolfsson et al. 2004). This has been particularly relevant in recent decades, when information on what one 'should and should not' do to have an optimal pregnancy has been so readily available online – and, overwhelmingly so, based on claims that are not scientifically validated (Bick 2010; Lee, Sutton and Hartley 2016; Luce et al. 2016; Song et al. 2012). Content sources vary widely from reality television to sensationalistic tabloid headlines, where pregnancy and birth are often depicted as traumatic experiences (Morris and McInerney 2010). Many women are unable to critically engage with the narratives portrayed, thus taking what they see or read as factual as opposed to anecdotal, which may reinforce fears of not having an 'uneventful' pregnancy (Luce et al. 2016). In addition, most women do not discuss the information they obtain online or through other media with their health care providers, which could further perpetuate misinformed notions about pregnancy and childbirth (Sayakhot and Carolan-Olah 2016).

The feelings of guilt and despair that follow a miscarriage carry a significant risk of psychological illness for both women and men (Hunter, Tussis and MacBeth 2017). Indeed, studies show that early miscarriages are associated with high rates of depression and anxiety among couples (Huffman, Schwarts and Swanson 2015). The vast majority (up to 80 per cent) will carry uncomplicated future

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pregnancies which result in the birth of babies who are alive and well, but it is often the case that women with a previous miscarriage worry about the chance of miscarrying in a future pregnancy. In fact, recent data show that depression and anxiety associated with a previous miscarriage tend to persist even after women give birth to a subsequent healthy child (Blackmore et al. 2011). In turn, this is thought to have an impact on rates of postpartum depression, as well as long-term implications on maternal-infant attachment, cognitive development and childhood behaviour (Murray et al. 2006).

Medical Technology and Impact on Pregnancy Experience

Using women's urine as a means to diagnose pregnancy goes as far back as ancient Egypt, where the sprouting of wheat and barley seeds watered with urine from a woman suspected to be pregnant was seen as a positive test (Haarburger and Pillay 2011). However, it was only once symptoms began – morning sickness, uterine growth and eventually foetal movements – that pregnancy was confirmed. The advent of endocrinology in the late nineteenth century introduced the notion of pregnancy-associated hormones, but it wasn't until the 1920s that human chorionic gonadotropin (hCG) became known as the specific hormone of pregnancy (Gnoth and Johnson 2014). Subsequent laboratory tests were developed using rabbits, frogs and rats with a view to detect urinary chorionic hormone. These were rudimentary at first, producing slow and unreliable results. In the 1970s, scientists were able to identify that only the beta-subunit of the hCG molecule is biologically active, which in turn led to the development of more sensitive antibody-based assays and home pregnancy tests in 1978 (Haarburger and Pillay 2011). Today, the use of home pregnancy tests (HPTs) has spread widely across the world, with some being nearly as sensitive as laboratory-based blood measurement of hCG. The sensitivity of these tests has been improved in recent years, which has resulted in earlier and earlier testing being possible. Indeed, some manufacturers claim high accuracy for tests performed as early as two to three weeks of pregnancy – well before the first missed period, when hCG levels are as low as 10 international units (IU) (Gnoth and Johnson 2014).

The shift from identifying a pregnancy based on symptoms to using serum and urinary markers introduced the notion of biochemical

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pregnancy, characterized by a positive pregnancy test before a gestational sac can be identified on ultrasound examination (Nguyen and Wilcox 2005). The vast majority of early miscarriages occur in the pre-clinical stage, where symptoms are still not present and historically women did not suspect or know that they were pregnant (Benagiano, Farris and Grudzinskas 2010). At around five to six weeks of pregnancy, clinicians expect to be able to visualize a gestational sac using ultrasonography. Once a gestational sac is seen with ultrasound scanning, the term 'clinical pregnancy' applies.

Ultrasound imaging was first used to diagnose pregnancy in the 1950s, and it has since evolved substantially (Whitworth, Bricker and Mullan 2015). Its use relies on the principle that sound waves whose frequency is above the audible range of human hearing will bounce when directed at body structures, hence revealing their morphology. When kept at low power and for short periods of time, ultrasound waves are deemed safe to the human foetus (Torloni et al. 2009). Ultrasonography is widely used for obstetric scanning across the world and has been enthusiastically received by pregnant women as it provides them with visual confirmation of pregnancy. Moreover, it may contribute to establishing a first connection between parents and foetus while reassuring women that their baby is well (Garcia et al. 2002; Littlewood 1999; Roberts et al. 2015; Whitworth, Bricker and Mullan 2015).

Modern ultrasound imaging has made it possible to diagnose embryonic miscarriages, even before the visualization of foetal heart activity, but also anembryonic pregnancies which can be identified prior to the symptoms of miscarriage (pelvic cramps and bleeding). Alongside biochemical testing, ultrasonography has revolutionized the way clinicians approach early pregnancy and miscarriage. However, ultrasound can also be a source of considerable distress and anxiety. When women present with abdominal pain or bleeding prior to six weeks of gestation, for example, it is often impossible to identify an embryo or a beating heart and a repeat scan is usually required a week later. Not only does this fail to provide women with reassurance, it may further exacerbate feelings of anxiety (Garcia et al. 2002; Roberts et al. 2015).

In women who present with vaginal bleeding or abdominal pain in the context of a positive urinary pregnancy test, clinicians will in the first instance quantify the blood level of hCG. If ultrasonography fails to demonstrate a gestational sac, this may indicate that the woman has either completely miscarried or that a pregnancy exists outside the uterus (termed 'ectopic pregnancy') and is thus

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non-viable. In such circumstances, clinicians usually rely on clinical symptoms and trends of blood hCG levels to monitor patients – a significant drop in hCG is deemed consistent with miscarriage, whereas plateauing hCG levels raise the suspicion of an ectopic pregnancy (NICE 2012a).

Concomitantly to biochemical testing and ultrasonography, contemporary perspectives on pregnancy in the UK have been markedly shaped by assisted reproductive technology (ART) – that is, the employment of techniques that aim to achieve pregnancy without the need for sexual intercourse. ART is used to treat subfertility, which in the UK refers to the inability to conceive despite having regular unprotected intercourse for at least one year (NICE 2013). Approximately one in six couples experience subfertility. Although the majority will end up conceiving spontaneously within one to two years, 7 per cent of couples do not conceive within two years of trying and may be offered some form of ART (Kamel 2013). A number of reasons are thought to lead to subfertility – female factors such as ovulation disorders and tubal blockage are implicated in up to 45 per cent of cases, and 30 per cent result from male factors (e.g. hormonal abnormalities or lack of sperm) (Brugo-Olmedo, Chillik and Kopelman 2001; NICE 2013). In up to a third of couples no obvious cause is found for their infertility (NICE 2013). Depending on the reasons behind a couple's subfertility, different ART approaches may be used – including intrauterine insemination, in vitro fertilization, intracytoplasmic sperm injection, donor insemination and egg donation.

In the late 1960s, Edwards, Bavister and Steptoe initiated efforts to develop a technique whereby eggs were extracted from ovaries and mixed with sperm in a laboratory setting (Edwards, Bavister and Steptoe 1969). Once an egg was fertilized in vitro, it was then transferred back into the woman's uterus in hopes of achieving implantation and subsequent pregnancy. This technique, called in vitro fertilization (IVF), first resulted in a live human birth in the United Kingdom in 1978 (Edwards and Steptoe 1978). Since then, further advances have made it possible to directly inject one sperm cell into one egg, in what has been termed 'intracytoplasmic sperm injection' (ICSI).

ART has been the subject of much controversy and discussion since its very inception, due to ethical, religious and legal factors (Harper et al. 2013; Kovacs 2003). Public debate has been generated on a number of issues, including the artificial 'creation' of life, gamete donation, surrogacy, same-sex couples and single women,

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posthumous use of frozen sperm or embryos, use of surplus embryos in research, or even the cost constraints associated with providing ART in the context of a publicly funded national health system (Harper et al. 2013; Human Fertilization and Embryology Authority [HFEA] 2010). The need to develop appropriate legislative frameworks in such a rapidly evolving field led to the creation of the HFEA in 1990. The HFEA has since been strictly regulating ART as well as providing patients with evidence-based information in the UK, in conjunction with the Royal College of Obstetricians and Gynaecologists (RCOG) and NICE (HFEA 2010). Many other advances have been made recently in the field of ART, including the ability to test the DNA of IVF-conceived embryos for genetic abnormalities prior to embryo transfer, in what is termed 'pre-implantation genetic diagnosis' (PGD) (Geraedts and De Wert 2009). This has been used to select embryos free of inherited diseases such as haemophilia, for example – and, controversially, for social sex selection. While many countries prohibit sex selection in IVF for non-medical reasons, in some this remains a nebulous field where no legislation or guidance exists (Kovacs 2003).

ART is not always successful. Despite significant technical developments, the chance of having a live birth following an IVF cycle is at best 30–40 per cent, although considerable improvements have been seen in the past decade (Wade, MacLachlan and Kovacs 2015). The main predictor of success remains maternal age – indeed, success rates decline to less than 20 per cent in women who are thirty-eight years of age or above and less than 5 per cent above forty-four (Lean et al. 2017; Yeh et al. 2014). Moreover, these figures can vary significantly between IVF clinics, which may derive from the use of different local protocols. Importantly, IVF centres may not always be transparent in how they report success rates – indeed, some will quote inflated pregnancy rates which do not necessarily mean a higher chance of having a live baby, as some of those will only be biochemical pregnancies which do not progress and eventually miscarry. However, the HFEA demands that clinics submit all their data and publish live birth rates per embryo transferred (HFEA 2010).

In the UK, funding for IVF is limited to a small number of cycles and depends on strict criteria (e.g. maternal age, existence of previous offspring) – in stark contrast with Israel, for instance, where unlimited cycles of IVF are offered to all Israeli women with up to two children in a given relationship, until the age of forty-five, even if the woman already has living children (Simonstein et al. 2014). It

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is thus unsurprising that in the UK most IVF cycles are carried out privately, with costs that may be as high as £7000 per cycle (Pandey et al. 2014). Indeed, the field of ART is part-science, part-business – and a lucrative one. In the UK, more than fifty thousand cycles of IVF are performed every year (McLernon et al. 2016). The financial investment associated with ART adds to the psychological and emotional burden experienced by women undergoing fertility treatment, which in turn may put a significant strain on relationships. This is further exacerbated when IVF is unsuccessful and couples require multiple cycles. Complications associated with stimulation drugs in the context of IVF (e.g. ovarian hyperstimulation, poor ovarian response, intra-abdominal organ injury during egg collection) also remain an issue. Moreover, as explained above, falling pregnant through ART does not necessarily mean carrying it to term or taking a live baby home, as approximately 20–30 per cent will miscarry, although the age-related risk of miscarriage after IVF is the same as for spontaneous pregnancy (NICE 2013).

In 1 to 3 per cent of couples, infertility presents in the form of recurrent miscarriages – that is, three or more consecutive pregnancy losses before 20 weeks of gestation, regardless of whether conception occurred through natural means or ART (Quenby et al. 2002). Despite modern advances and detailed investigations (which include testing parental DNA and, when possible, the genetic makeup of the miscarried foetus), clinicians are unable to identify a cause for recurrent miscarriage in the majority of cases (RCOG 2011). Autoimmunity is thought to play a significant role in the aetiology of recurrent miscarriage, and a number of adjuvant therapies (including aspirin, anti-coagulants and immunosuppressive steroids) have been employed in an attempt to improve pregnancy outcomes, although not always successfully and often without adequate scientific evidence (Jeve and Davies 2014).

Conclusion

Technological advances have played a crucial role in the way people perceive pregnancy. For centuries, only the cardinal symptoms of morning sickness and uterine growth would reveal a woman's pregnant state. In the early twentieth century, biochemistry contributed significantly to identifying pregnancy-specific hormones and developing immune-based assays that made the diagnosis of pregnancy easy and affordable to women at an early stage and in

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privacy. The introduction of ultrasound into obstetric care, in the 1950s, has made it possible for women to visualize their babies in utero, somewhat conferring a more concrete dimension to the developing foetus several weeks before it becomes viable. While ultrasound has had a powerful impact upon pregnancy care worldwide, it has also significantly shaped the way women and those around them experience pregnancy loss. Miscarriage is no longer a self-declared event through which one's body expels an abnormal foetus – it now involves visualizing the absence of a baby's heartbeat on a computer screen often prior to abdominal pain or bleeding.

Over the past decades, the care of women with early pregnancy loss in the UK has sustained significant improvements, with the introduction of dedicated clinics that aim to provide efficient and compassionate care while minimizing hospital admissions and life-threatening complications. Moreover, a rise in the age when women decide to become mothers has had a profoundly negative impact on conception and miscarriage rates, making way for assisted reproduction. Becoming pregnant is now seen by many as an emotional and financial endeavour which, when unfulfilled, may generate feelings of frustration and shame. In a world filled with mediatic advice that is not always evidence-based, misconceptions on miscarriage and fertility are often perpetuated, thus prompting couples to spend more time, energy and financial resources on achieving their fertility aspirations, sometimes to the benefit of private enterprises.

In the ever-evolving field of early pregnancy, awareness of miscarriage and its powerful consequences on women's health has been rising. Women are now empowered to make informed choices about their pregnancies, and clinicians are expected to address the reality of miscarriage in a sensitive and holistic manner that takes into account the woman's knowledge, preferences and wider social context.

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