Advances in Clinical Obstetrics and Gynecology

Volume 2

Edited by
Howard J. Osofsky, M.D., Ph.D.

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Preface

In Volume 1 of this series, I commented on the major advances in knowledge and technology—and the resultant profound changes in clinical practice—that have occurred in the specialty of obstetrics and gynecology in recent years. To compare current approaches to treatment and standards of practice with those that were accepted just 10 to 15 years ago is at times mind-boggling. At times, obstetricians and gynecologists may feel beleaguered by changing patient expectations, unwarranted criticisms, ever rising bureaucratic demands and paperwork, and increasing malpractice litigation. Yet, no group has responded more effectively—developing techniques to allow more couples to embark on a pregnancy, decreasing perinatal risk and perinatal mortality, improving the outcome for high-risk neonates, allowing couples more choices concerning their reproductive function, providing new approaches for evaluation of symptoms and maintenance of well-being, and delivering better and more sophisticated treatment for a variety of conditions. So numerous and rapid have been the advances that it is difficult to keep abreast of them theoretically and technically. And this condition is likley to continue in the future.

It is our hope that the volumes in this series will be of help in providing important information about the current state of knowledge in key areas, helping clinicians to keep abreast of new developments and what may be expected in the near future. We will make every effort to keep the topics and material clinically relevant and forward-looking. I would like to stress that we are very much influenced both by our readers' suggestions about topics and contributors that should be included in the series and by their evaluations of how well the chapters are meeting the stated goals of the series. This volume to a considerable extent reflects a number of readers' suggestions. We hope that the suggestions and comments will continue. They will play a key role in helping to make the series a meaningful one for all of us.

Howard J. Osofsky, M.D., Ph.D.

Acknowledgments

There are a number of people to whom I would like to express special appreciation for their contribution in making the second volume a reality—a volume which I believe is of high quality. First I would like to thank the contributors. I have given individuals who are experts in their area and who are very busy the task and challenge of pulling together important material in a clinically relevant manner. Inspite of their schedules and other commitments, they have enthusiastically met the challenge and worked hard at preparing meaningful chapters. I sincerely appreciate their efforts.

I further appreciate the efforts of Dr. Raja Abdul-Karim, my close friend and colleague for many years. He has made valuable contributions in helping to think through the volume and the appropriate chapters and contributors. As with the last volume, Marjorie McElhenny contributed much after-work time to help me coordinate, pull together, and reread contributions to the present volume. My wife, Joy, by her patience, cooperation and tolerance of my long hours has continued to provide the climate which is essential to make this type of endeavor a possibility.

Finally, I want to thank you, the readers. Your enthusiastic acceptance of the first volume and your suggestions for the second volume have helped immeasurably in thinking through and beginning a new series. I will look forward to your comments and advice in our future efforts for this series.

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Contents

CHAPTER 1

A Program for Human *in Vitro* Fertilization and Embryo Transfer

HOWARD W. JONES, JR., M.D.

INDICATIONS

The use of *in vitro* fertilization and embryo transfer in the human is to be considered only when all other methods of therapy have been exhausted. There are five main indications: (1) irreparable or absent fallopian tubes, (2) oligospermia, provided a sufficient number of actively motile sperm are available, (3) hostile cervix, (4) the normal infertile couple, and (5) endometriosis which has continued to cause infertility in spite of previous surgical or medical therapy.

INEFFICIENCY OF HUMAN REPRODUCTION

To understand the odds of achieving pregnancy in any single cycle by *in vitro* fertilization and embryo transfer, it is necessary to realize that human reproduction is inefficient. In this field there have been a number of studies well-summarized by Biggers (1). Depending on the study, the expectation of pregnancy in any single normal cycle of adequate exposure seems to vary from about 25% to no more than 31%. The nonfertile cycles are the result of failure of an oocyte to fertilize in spite of its being exposed to sperm or the development of an abnormal embryo which either does not implant or is aborted. It is unlikely that a program of *in vitro* fertilization could exceed the normal expectancy of fertilization unless multiple oocytes are obtained during a single cycle and multiple embryos are transferred.

REQUIRED INVESTIGATIONS

Most patients will require as a minimum preprogram work-up a screening laparoscopy to ascertain the availability of the ovaries. In addition to that a current hysterogram is absolutely essential to be certain that there are no abnormalities of the uterine cavity. It has been found, for example, that patients who have been exposed *in utero* to diethylstilbestrol (DES) have a high frequency of ectopic pregnancy and, among patients with bilateral ectopic pregnancies, it is necessary to be certain that the uterine cavity is not deformed from the DES. This can sometimes happen, even though the patient is unaware of DES exposure. An andrology survey of the husband is a key point in the investigation not only to determine the adequacy of actively motile sperm but also to be certain that there is no subtle infection, as, for example, with *Ureaplasm urealyticulum*. Although the role of the latter organism is unclear at the moment, it is a treatable problem, and for that reason it

seems important to be certain that no infection exists.

PATIENT SELECTION

The patients selected are obviously those who fall within the indications listed above. Over and above that, the couple must be emotionally capable of experiencing the rather rigorous protocol required for such a program. It goes without saying that laparoscopically the ovaries must be available, that the uterus must be anatomically normal, and that the menstrual cycle must be dependable or capable of being made dependable by the use of stimulation. It is difficult to be specific about the upper age at which the program is not advisable. In view of the fact that natural fertility seems to begin to decline at about the age of 35, it is certainly preferable to have younger patients. On the other hand, there seem to be individuals who are not as old biologically as they are chronologically, and under such circumstances they are acceptable. It needs, of course, to be realized that fetal abnormalities begin to increase at the age of 35, so in general one would hope to include patients above the age of 35 only in exceptional circumstances.

HARVEST CYCLE

Assuming that the patient is acceptable from all points of view for the program, there are several options with respect to harvesting the oocyte. It may be done (1) in the natural cycle, (2) in the natural cycle except for the use of hCG to substitute for the normal midcycle LH surge, (3) in a cycle stimulated by Clomid or Clomid plus hCG, or (4) in a cycle stimulated by hMG plus hCG.

Natural Cycle

Historically, Edwards and Steptoe (2) worked initially with stimulated cycles but were unsuccessful and found that success was obtained by the use of the natural cycle. For this reason there has been considerable experience with the natural cycle. It has certain disadvantages. The main one concerns fickleness in the harvest cycle. Patients who menstruate regularly often delay their ovulation or sometimes suppress it for a very considerable period apparently due to the stress associated with the procedures involved in diagnosing the precise time of ovulation. Methods for determining the optimum time for oocyte aspiration have depended on the identification of the LH surge. Edwards and Steptoe and others have preferred to use the HI-gonavos urinary assay for LH and have routinely harvested the oocyte prior to 28 hours after the initiation of the LH surge. This requires capability to carry out the aspiration anytime day and night, 7 days a week. To a certain extent, this can be modified in view of the discovery in the early part of 1981 that prematurely harvested oocytes not only can be maintained in culture for several hours prior to their fertilization but also, in fact, benefit by such preincubation. Therefore, it is possible to have a schedule which carries out oocyte aspiration to a certain hour in the evening, as, for example, 8:00 P.M., and then to resume activities in this regard first thing in the morning.

An alternate method of timing the aspiration at midcycle is to use hCG injection to substitute for the spontaneous LH surge. The technique here is to follow the development of the follicle by ultrasonography, to give an injection of hCG when the follicle reaches about 17 mm in diameter, and then to schedule the follicle aspiration 36–38 hours subsequent to the hCG injection. It is possible therefore to manipulate to a certain extent the timing of the hCG injection so that aspiration is performed at a convenient hour and can be scheduled in the operating room. At this writing there are insufficient data on the efficiency of this modification of the normal cycle. Suffice it to say, in the experience of the Norfolk effort, mature oocytes have been obtained under this circumstance. On the other hand, a patient may trigger her own LH surge prior to the injection of the hCG, and ovulation has been found to have already occurred at laparoscopy 36 hours after the hCG injection.

Clomid plus hCG

Several programs have pioneered the use of 100–150 mg of Clomid for 5 days beginning on day 3 or 5 of the spontaneous cycle, with the thought that this would recruit more than one dominant follicle and that there would therefore be codominant follicles, thus providing the opportunity to secure more than 1 preovulatory oocyte. In the experience of Wood et al. (3) an average of 2.1 oocytes/cycle were obtained by this method. There seems to be a certain fickleness of response to the Clomid,

so that it has been estimated that between 10% and perhaps as many as 20% or even a higher percentage of patients do not give an expected and hoped for response to the Clomid administration. This has led to the supplementation of the Clomid technique with minimal doses of hMG and with the use of hCG to substitute for the midcycle LH surge.

hMG plus hCG

An alternate method of stimulation is to use hMG rather than Clomid for the purposes of recruitment and development of multiple follicles. The theoretical basis for preferring this method to the use of Clomid is related to the experience with the use of these substances in normally anovulatory women. Under this circumstance the incidence of miscarriage after pregnancy seems to be less in the hMG-stimulated cycles than in the Clomid-stimulated cycles. It remains to be determined if this advantage holds over to the use of hMG in the normal cycle. The technique has been given in detail for this in another publication (4). Basically, in a patient with a normal 28-day cycle the protocol specifies the use of 2 ampules of hMG beginning on day 3. Her clinical parameters of cervical mucus score plus the shift in the maturation index of the vagina and her serum extradiol (E_2) are followed on a daily basis. The hMG stimulation is discontinued based on a protocol which considers various eventualities. hCG is given to substitute for the LH surge under certain specifics of the protocol, and oocyte aspiration is scheduled 36 hours after the hCG injection. With this technique, 2 or, frequently, 3 preovulatory oocytes can be obtained (Table 1.1).

OOCYTE ASPIRATION

Various techniques have been suggested for the aspiration of oocytes. Steptoe and Edwards prefer a 3-puncture technique, as do the groups at Melbourne. Various types of needles have been used. The Teflon-lined needle and aspiration set devised by Renou et al. (5) seems to be quite efficient. In the program at Norfolk, it was determined that a needle with an inside diameter of 2.25 mm was much more efficient than other techniques that had been used. A very high percentage of recovery by use of such a needle with a 2-puncture technique with an operating laparoscope has been reported (6).

IN VITRO FERTILIZATION AND CULTURE

A most important discovery was the documentation that incubation of the oocyte for a number of hours prior to exposing it to sperm was a very desirable thing. This is reasonable. After all, the oocyte is obtained from the preovulatory follicle prior to spontaneous ovulation. Presumably, additional steps in maturation are in progress. These apparently are completed *in vitro*. The extreme limits of such incubation remain to be determined, but the experience in the Norfolk program would suggest that oocytes are viable for as long as 24 hours and similar unpublished information is available from other programs. While the situations are not exactly comparable, it is very likely that this is not an unnatural situation. Otherwise, for normal pregnancy it would be necessary for sperm to be available in the female generative tract at ovulation.

As a routine, the Norfolk program preincubates eggs for a minimum of 6 hours, but in the event the cumulus seems to be less than completely expanded the incubation of the oocyte is allowed to proceed for up to 24 hours. It is possible that this period of incubation could be extended. It seems to be a mistake to introduce sperm to the immature oocyte, since the cortical granules are apparently not yet completely developed, and it is under this circumstance that polyspermia may occur. In one oocyte, for example, 5 pronuclei were noted in an oocyte which was very premature but which was nevertheless placed with sperm before it was understood that this was an undesirable procedure.

The medium used for culturing oocytes does not seem to be critical in that a variety of culture media have been found to be satisfactory. Ham's F-10, Earle's, and others supplemented by heat-inactivated human serum have all been used successfully. It may well be that the ideal medium has not been identified because there is a suspicion that the rate of cell division *in vitro* is less than that *in vivo*. Particularly impressive data on this point have been developed for the monkey by Kreitmann and Hodgen (7). Similar data are understandably unavailable for the human, but it would seem remarkable if it were otherwise than as noted in the monkey.

EMBRYO TRANSFER

There are two main issues in embryo trans-

Table 1.1
hMG-hCG Protocol

General

1. The clinical parameters, blood for E_2 and any other assays, and ultrasound are performed at approximately 8:00 A.M.
2. All medications, such as hMG, should be given at about 4:00 P.M. so that advantage can be taken of the assays performed on the 8:00 A.M. blood.
3. hCG should be given at 6:00 P.M. with a laparoscopy posted at 7:30 A.M., 37½ hours later, so that by the time the egg is harvested, it will be about 38 hours.

Day 3 (day 5 if a long cycle)

8:00 A.M. The clinical parameters, blood, and ultrasound are obtained.
4:00 P.M. Two ampules of hMG are given.

Days 4 and 5

8:00 A.M. The clinical parameters and ultrasound may or may not be repeated, depending on the clinical situation, but no blood need be taken on these days.
4:00 P.M. Two ampules of hMG are given.

Days 6 and each day until hMG is discontinued

8:00 A.M. The clinical parameters, blood, and ultrasound are obtained.
4:00 P.M. Two ampules of hMG are given.

Indications for the discontinuation of hMG

hMG should be discontinued on the day when the E_2 is 300 pg/ml or more and the clinical parameters have shifted for at least 1 day,

or

E_2 reaches 600 pg/ml without a shift in clinical parameters,

or

the clinical parameters have shifted for 3 consecutive days regardless of the level of the E_2,

or

by ultrasound study the enlargement of the largest follicle has been steady and has reached 14 mm in diameter.

Indications for administration of hCG

The hCG will be given 50 hours after the last hMG if the E_2 continues to be greater each day after the discontinuance of hMG,

or

the largest follicle has steadily progressed and has reached 18 mm in diameter.
The hCG will be given at 74 hours in all other circumstances.

General

The clinical parameters, blood, and ultrasound are to be continued at 8:00 A.M. daily through the day prior to laparoscopy, beginning with day 6. On the day of laparoscopy, blood will be drawn at the time of laparoscopy for such assays as seem appropriate.

fer. The first is the question of when it should be done, and the second is how it should be done.

Evidence from Diaz et al. (8) would suggest that under normal circumstances the embryo reaches the uterus somewhere between 4 and 6 days after ovulation. If the concept is to mimic nature insofar as possible, this would mean that the embryo should be cultured *in vitro* until this time. It has already been mentioned that *in vitro* fertilization probably results in some delay in cell division, and for that reason it has been the practice to transfer the embryo at earlier times. Various times have been tried, but in the Norfolk program from the beginning the concept was to use early transfer in the hope that the intrauterine environment would be as favorable as and perhaps even more favorable than the *in vitro* culture medium. Thus, the current practice is to transfer at the 4-cell stage which is usually about 44 hours. Pregnancies clearly can occur when this is done, but additional data would be useful for various other times of transfer. However, it is unlikely that meaningful data in this regard will be collected for a considerable period of time.

The current practice in almost all programs is to use transcervical transfer. This goes against animal data because it has been gen-

erally appreciated in animal husbandry that surgical transfer through the fundus carries a greater success rate than transcervical transfer. However, difficulties in the practicalities of transfundal transfer in the human have precluded its use at least up to this time. In the Norfolk program a small Teflon catheter is passed through the cervix with the patient in the knee-chest position. Generally, the patient is unaware of the passage of the transfer catheter. The catheter is passed for a predetermined distance which is calculated to have the eye of the transfer catheter about 1 cm from the top of the fundus. The embryo is transferred to the fundus with 0.2 ml of culture fluid, followed by about an equal amount of air to assure that the embryo has been ejected from the catheter. The catheter is withdrawn after a few seconds while it is rotated 180°, in order to try to prevent the withdrawal of the oocyte with the catheter. The catheter and the flushings of the catheter are examined microscopically, and in the absence of the embryo it is assumed that the embryo has been deposited at the fundus of the uterus.

The patient is requested to remain in the prone position for a minimum of 4 hours following the transfer.

OBSTETRIC CARE

The main issue in the immediate transfer period is whether progesterone support for a potential luteal phase defect is appropriate. The concern about the luteal phase stems from the effect of aspiration of the follicle on the function of the corpus luteum. Data from spontaneous cycles indicate that in some cycles there may be some deficiency, although on average this does not seem to be a prominent feature (9). Therefore, in the absence of serum progesterone determinations it is difficult to know which cycle might be expected to be deficient. Some knowledge of the patient's previous history may be helpful in this regard. The disadvantage of supplementing all cycles is not only the unnecessary use of progesterone but also the possible delay in the subsequent menstrual period by this technique. With the use of ovulatory stimulants and the development of multiple follicles the progesterone secretion by the ovary is greatly in excess of normal. For this reason, with multiple follicles it is less likely that a true luteal phase defect will occur. It is interesting that it has been noted that with hMG stimulation the luteal phase is sometimes shortened (2). However, during the shortened phase, the serum progesterone values are greatly in excess of those experienced during the normal cycle. In patients who have become pregnant during stimulated cycles, the progesterone recovers promptly apparently from the hCG of the early embryo, so that from a practical point of view the shortening of the luteal phase in the stimulated cycles may not be of practical significance.

After the pregnancy is well-established, no special precautions seem to be required for the obstetric care.

There is a question of whether amniocentesis should be routinely recommended in patients who become pregnant by virtue of *in vitro* fertilization. There is, of course, always concern about whether children so conceived will have a greater-than-normal expectancy of congenital defects of various kinds. However, the experience to date is reassuring in this regard, and there are no animal data which would lead one to believe that this should be a problem (10). Therefore, the current attitude is that amniocentesis is not necessary unless there is an indication from an obstetric point of view that this should be carried out.

RESULTS

By the end of 1980, only 2 children had been born by the process of *in vitro* fertilization and embryo transfer (11).

In 1981, Wood et al. (3) reported on 152 aspiration cycles. They harvested eggs in 130 or 85%. Fertilization occurred in 103 or 79% of the harvested eggs and in 68% of the aspirated cycles. Embryo transfers occurred in 91 or 88% of the fertilized eggs, 70% of the harvested eggs, and 60% of the aspirated cycles. Pregnancies occurred in 15 patients or 16.5% of all those transferred, 15% of those fertilized, 11.5% of the harvested eggs, and 10% of the laparoscopic aspirations.

In Norfolk from September 27, 1981 through October 15, 1982, 190 consecutive laparoscopies were done in patients who had been stimulated by hMG/hCG. In 158 of these, or 83%, fertilizable eggs were obtained. In 152 of these cycles, or 80% of the laparoscopies and 96% of those cycles in which fertilizable eggs were obtained, the eggs were, in fact, fertilized. However, transfers occurred in only 140 of the 190 cycles. This was 74% of the patients who were laparoscoped and 89% of those from

whom fertilizable eggs were obtained. There were 36 pregnancies. This represents a pregnancy rate of 19% based on laparoscopies and 26% based on transfers.

These results are representative of those obtained during 1982. Several other clinics with a relatively large volume, such as from the two clinics in Melbourne and the clinic in Cambridge, England, have orally reported results which are very similar.

The inefficiencies brought out at the various steps of the process, specifically those of fertilization and the development of embryos suitable to transfer, may well be an expression of the inefficiency of human reproduction.

However, the fallout after transfer is probably an expression of method failure and represents both the greatest problem and the greatest opportunity for improvement in the results of *in vitro* fertilization and embryo transfer.

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CHAPTER 2

Evaluation and Management of Threatened and Habitual First Trimester Abortion

RICHARD P. DICKEY, M.D., PH.D.

The application of real-time ultrasound to early pregnancy has greatly increased knowledge about the status of the conceptus during the first 3 months of pregnancy. In more than 50% of spontaneous first trimester abortions followed with real-time ultrasound and reported in this chapter, embryonic development with detectable fetal heart rate (FHR) was evident between the fifth and seventh week of gestational age.[14, 15] The term "blighted ovum" is now reserved in our clinic for abortions in which embryonic growth and FHR have never been detected. The terms embryonic demise and fetal demise are used for abortion in which a crown/rump length and FHR have been detected earlier. In many cases, specific problems which may contribute to embryo and fetal demise are detectable by ultrasound.

Modern-day chromosomal studies and earlier histological studies[6, 37] support the ultrasonic evidence that large numbers of spontaneous abortuses may be chromosomally normal. Chromosomal analysis techniques found that 50–60% were chromosomally abnormal.[16, 17] In a large study, the risk of spontaneous abortion in a second pregnancy was found to be only 7% if a chromosomal abnormality was present in the first abortion, and therefore equals the risk of abortion among women whose first pregnancy was normal, whereas the risk of a second abortion was 24% if the first abortus was chromosomally normal.[6] One explanation of this apparent paradox is that when the abortus in the first pregnancy is chromosomally normal, the abortion is more likely to be the result of a chronic maternal problem.[28] Midtrimester abortions with no chromosomal abnormalities are also more likely to be the result of maternal abnormalities.

At one time it was believed that the risk of abortion increased with each spontaneous abortion. After the third abortion, the risk was believed to be 75%.[57] The possibility that a spontaneous abortion will occur again in a subsequent pregnancy has been reassessed by modern authors.[30, 62, 89] Following one spontaneous abortion, the risk of a subsequent abortion is approximately doubled from 12.3% to 23.7%.[89] The risk of subsequent abortion does not increase significantly after the second abortion. After the fourth abortion, the risk of an abortion in the next pregnancy is only 25.6%.[89] On the basis of this information, evaluation of the possible cause of abortion should begin after even one spontaneous abortion.

In view of the ultrasound and chromosomal evidence that the early embryonic development of many spontaneous abortuses is normal as often as it is abnormal and the evidence indicating that the risk of repetitive abortions is increased to the maximum after the first abortion, there is a need to reassess the management of threatened and repeated abortions. In the remainder of this chapter, the causes of abortion are grouped into the six categories of hormonal, anatomical, infectious, chromosomal, hematological, and toxicological for review. Identification and correction of some of these nongenetic factors may enable the prevention of some abortions. Practical steps that can be used in the management of threatened abortions include the assessment of embryonic, ovarian, and placental status by ultrasound and progesterone studies. Unfortunately, the clinically recognizable symptoms

of threatened abortion, bleeding, cramping, and failure of uterine growth, often occur too late, after embryonic or fetal demise has already taken place. Even so, the knowledge gained in evaluation of one abortion may be used to prevent a recurrence. A plan for the evaluation of nonpregnant patients with a history of previous abortion and specific methods of treatment for the recognizable causes of repeated abortion are presented.

DEFINITIONS

Abortion is the expulsion or removal of the products of conception from the uterus before the attainment of fetal viability. The abortus may be alive or dead. Viability is variously described as 400 gm, 500 gm, or 20 weeks.[68]

During the first week after ovulation and fertilization, the products of conception are designated as the *fertilized ovum*. The *embryonic period* is taken as starting at the beginning of the second week after ovulation and coincides with the expected time of implantation. Neither the sac nor the embryo can be seen by ultrasound at this time. At the beginning of the fourth week, gestational day 22, the sac measures 5 mm by ultrasound, and the embryo, which still cannot be detected, measures approximately 1 mm.[27] The end of the embryonic stage and the beginning of the *fetal period* are arbitrarily considered to occur at the beginning of the ninth week after ovulation, when all major structures have formed. At this time, gestational day 57, the embryo measures 27 ± 4.3 mm crown/rump length.

Gestational age is measured from the beginning of basal body temperature rise about the 14th day in most 28-day cycles. Menstrual age begins with the first day of normal menstruation, disregarding premenstrual spotting, if any. Actual dates are given as weeks and days from ovulation, thus day 16 after ovulation is also gestational week 3, day 2, and menstrual week 5, day 2, assuming a 13-day preovulatory phase.

Development of the fetus may also be defined in terms of stages, as described by Streeter, for the Carnegie collection of early embryos.[80] Limb buds appear at stage 13, crown/rump length 4–6 mm, gestational age 28–32 days. Limb development is completed and movement may be discerned at stage 23, crown/rump length 27–31 mm, gestational age 56–60 days. At about stage 17, crown/rump length 11–14 mm, gestational age 42–44 days, the embryo begins to uncurl from a C-shaped form to more of an E-shaped form, with the center being the umbilical vessels.[27] The increasingly rapid growth of the embryo, in comparison to the vessels, is one cause of straightening at this time. Prior to this time, the crown/rump length increases at a rate of approximately 0.5 mm/day. After this time, the length increases at a rate of approximately 1.1 mm/day.[14]

The *first trimester*, by definition, encompasses the first three lunar months of pregnancy from gestational age 1 through 84 days, or up to 98 days menstrual age. In practical terms, spontaneous abortions due to failure of embryonic development (blighted ovum) are usually completed by the end of the 12th gestational or 14th menstrual week.

Second trimester abortions are those which occur from the beginning of the 13th gestational or 14th menstrual week until the beginning of possible extrauterine survival, between the 20th and 21st gestational week.

We reserve the term "*blighted ovum*" for those spontaneous abortions in which no embryo can be demonstrated either by ultrasound or histology. We use the term "*embryonic demise*" for abortions in which an embryo can be identified histologically or by ultrasound and which occur before the beginning of the ninth gestational week.

The term "*fetal demise*" is used for abortions which occur after the conceptus has begun the ninth week of development.

Threatened abortion is a term used when uterine bleeding of any amount or uterine cramping occurs. The term "threatened abortion" may also be applied when ultrasound findings of fluid surrounding the ovum sac or a FHR below 120 is observed.

Inevitable abortion is a term used when there is definite loss of a previously discernible FHR, when there is a diminution in size of the ovum sac before the stage at which a FHR or crown/rump may be discerned, or when the cervix has dilated with tissue in the os.

Missed abortion refers to the retained products of conception long after fetal or embryonic demise. There is no agreed upon length of time that demise must be present before the term "missed abortion" is used. Lengths of 4–8 weeks have been variously described.

Habitual abortion refers to repeated spontaneous abortion.