Obstetrics and Gynaecology Cases - Reviews

Angular Pregnancy: A Review of Cases Reported in the Past 80 Years

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Abstract

Objective: To review reported cases of angular pregnancy (defined in 1898 as "implantation of the embryo just medial to the uterotubal junction, in the lateral angle of the uterine cavity" [1]) to determine outcomes.

Study design: A systematic search of medical electronic databases (1934-2013; search term: "angular pregnancy") was performed, initially yielding 150 manuscripts; after application of selection criteria, 54 were included for review, yielding 85 cases of angular pregnancy. Pregnancy outcomes were analyzed overall and in time period subgroups (period 1 = 1934-1981; period 2 = 1982-2013).

Results: Overall, the live birth rate (LBR) was 21/85=25% and maternal death rate was 4/85=5%. There were 15 spontaneous abortions (15/85=18%) and two cases of fetal demise (2/85=2%). There were also 24 cases of uterine rupture (24/85=28%). 26 of the angular pregnancies were managed expectantly, yielding 18 live births (LBR=18/26=69%). The LBR was equivalent in time period one and two (15/61=25% and 6/24=25%, respectively). The only statistically significant difference between time periods was with spontaneous abortion, higher in time period one (15/60=25%) than in two (024/=0%) (p=0.0074).

Conclusion: While this study nevertheless represents the largest aggregation of angular pregnancy cases to date, given data limitations, perhaps the only reasonable conclusion is that more research is needed. Specifically, the prevalence and clinical significance of 'angular pregnancy' could only be properly determined by conducting a large prospective multicenter study with clearly defined diagnostic criteria – updated since 1981with special attention to how to differentiate angular from interstitial pregnancies on imaging -- and robust follow up.

Introduction

Angular pregnancy was first defined in1898 by American obstetrician Howard Kelly as "implantation of the embryo just medial to the uterotubal junction, in the lateral angle of the uterine cavity" and medial to the round ligament [1]. In 1981, Jansen and Elliot proposed the following criteria for angular pregnancy:

1) Clinical presentation with painful asymmetric enlargement of the uterus, followed by

2) Directly observed lateral distension of the uterus, with or without rupture, accompanied by displacement of the round ligament reflection laterally;

3) Retention of the placenta in the uterine angle [2].

One of the motivations for the current investigation is that despite its first description abortion or vaginal delivery; nearly 120 years ago, much remains unknown about angular pregnancy, not only because of the relative heterogeneity in which individual cases have been reported but also the small absolute number of cases reported. As a result, some clinicians may consider angular pregnancy an outdated term, while others may question its clinical relevance or whether it even exists as a real entity. However, recent articles in respected peer-reviewed journals reporting angular pregnancies suggest otherwise [3,4].

The topic of angular pregnancy is important because, as the criteria for angular pregnancy suggest, the condition is considered high risk because of the association with spontaneous abortion, uterine rupture and abnormal placental implantation; however, just *how* high risk remains unknown. Furthermore, the significant interval change in diagnostic imaging since 1981 when these criteria were proposed provides an impetus for critically reappraising the topic. Therefore, the purpose of this study was to perform a systematic review of angular pregnancy cases reported in the literature in order to determine pregnancy outcomes.

Materials and Methods

Sources

Because this was a review of cases reported in the literature, this study was exempt from Institutional Review Board approval.

We referred to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement as a guide for the methodological approach; however, since this study represents an

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analysis of individual (or groups of individual) cases reported – and is not a meta-analysis of randomized controlled trials or observational studies –PRISMA, MOOSE (Meta-analysis Of Observational Studies in Epidemiology), and STROBE (Strengthening The Reporting of Observational studies in Epidemiology) checklists are not applicable.

A systematic search (1930-2013; search term: "angular pregnancy") was performed by one of the authors by searching several biomedical electronic databases including PubMed, Medline, Embase, and The Cochrane Library. The languages covered included English, French, Italian and Spanish. Results were supplemented with references identified through bibliographies and related article searching.

Study selection

All eligible manuscripts were screened by a single reader based on title and abstract for possible inclusion in this study. Questions about final inclusion were resolved by consensus with a second reader. Specific inclusion criteria were manuscripts: 1) published in English, Italian, Spanish and French (the systematic search did not yield abstracts in any other languages and at least one of the authors were proficient to fluent in all of these) for which full texts were available; and 2) whose in-text description of angular pregnancy was consistent with the clinical criteria set forth by Jansen and Elliot listed above [5] and which included at least one case of angular pregnancy. Exclusion criteria for cases included definitions of angular pregnancy inconsistent with the above criteria and a lack of documented outcome.

For the purposes of consistently reviewing included cases and categorizing the outcomes, the following operational definitions, listed alphabetically, were utilized [6,7]:

- Fetal demise: death of fetus in utero at or beyond 20 weeks gestation

- Hysterectomy: subtotal or total surgical removal of the uterus performed due to uterine rupture, placenta accreta/percreta, or complications of initial management; this does not include partial resection of less than ½ the uterus

- Live birth: vaginal or Caesarean section delivery of an infant that survived at least one month

- Maternal death: death of the mother secondary to obstetrical complications during angular pregnancy, labor, or the puerpuerium, including exsanguination from uterine rupture and septic shock from endometritis

- Placental abruption: separation of the placenta from its implantation site before delivery of the fetus; cases were only classified as such if explicitly described in the literature

- Placenta accreta/increta/percreta: penetration of placental chorionic villi into or through the myometrium; cases were only classified as such if the term accreta, increta, or percreta were specifically mentioned.

- Retained placenta: lack of expulsion of the placenta within 30 minutes of delivery of the infant [8].

- Spontaneous abortion (miscarriage): unintentional termination of pregnancy prior to 20 weeks gestation, *not* including those ending secondary to uterine rupture.

- Therapeutic or elective abortion: elective termination of pregnancyat any point in gestation by any means.

- Uterine rupture: tear through all layers of the uterus occurring at any time in gestation and with any outcome.

Qualitative and quantitative study data was extracted from selected manuscripts using a predetermined data collection template. Specifically, from each case of angular pregnancy reported, the following data were recorded: age at presentation, gravity (including current pregnancy), parity (prior term and preterm deliveries with

any outcome), gestation in weeks at diagnosis (when given in months, we multiplied by an average month of 30 days before dividing by 7 to yield weeks), clinical presentation, prior known uterine pathology, obstetrical history (including known spontaneous or elective abortions and previous cesarean sections), and outcome. The main variable of interest was pregnancy outcome, which was categorized as live birth, spontaneous abortion, elective or therapeutic termination, fetal demise, placental abruption, placenta accreta/percreta, uterine rupture, hysterectomy, and maternal death. Outcome variables were not mutually exclusive (e.g., one angular pregnancy could result in both live birth and hysterectomy).

In terms of statistical analyses, means and standard deviations were used to describe continuous variables, while frequencies and percentages will be used to describe categorical variables. T-tests (general linear models) were used to compare continuous variables and chi-square tests were used to compare categorical variables. Pregnancy outcomes were analyzed overall and in time period subgroups, with time period one defined as 1934-1981 and period two as 1982-present; the rationale for this division in time was that 1981 was the last year a major review and meta-analysis on the subject was published [5]. An additional subgroup of interest was comprised of cases that were managed expectantly, because they offered insight into the natural history of this condition.

Results

Study selection

A total of 150 manuscripts were initially screened, of which 40 potentially eligible manuscripts were selected for further review. Specifically, from time period one (1934-1981) there were 20 manuscripts yielding 25 cases, and from time period two (1982-2013), there were 20 more manuscripts yielding 39 cases. References cited in the bibliographies of these 40 manuscripts yielded an additional 15 articles with 32 cases that met criteria. After excluding one duplicate manuscript with 10 cases [9], and one case for which there was no documented outcome, a total of 54 manuscripts [5,9-62] yielding 85 cases of angular pregnancy were included in the final systematic review; Appendix 1 summarizes how these 85 angular pregnancies presented, were treated, and their ultimate outcome.

Results

After pooling the 85 cases for analysis, the average age (of 69 available ages) of the subjects with angular pregnancy was 31 (range, 19-41). Overall angular pregnancy outcomes are summarized in Table 1, with highlights as follows: the 85 angular pregnancies were associated with 21 live births, corresponding with a live birth rate of 25%; there were 4 maternal deaths, corresponding with a maternal death rate of 5%; and there were 24 cases of uterine rupture, corresponding with arupture rate of (28%). Of the 21 live births, 18 were born alive after 32 weeks' gestation, and all 18 lived; three were born alive before 32 weeks' gestation – at 23, 25.6, and 30 weeks, respectively – but the first two expired within the first month of life. There were 15 spontaneous abortions (15/85=18%) and 2 cases of fetal demise (2/85=2%), one at the gestational age of 30 weeks and

Table 1: Overall Outcomes* of Angular Pregnancies (n=85).

Angular pregnancy outcome	N (%)
Live birth	21 (25%)
Maternal death	4 (5%)
Uterine rupture	24 (28%)
Abortion-spontaneous	15 (18%)
Abortion-therapeutic or elective	24 (18%)
Hysterectomy	22 (26%)
Placenta acreta/increta/percreta	5 (6%)
Retained placenta	3 (4%)
Placental abruption	1 (1%)
Fetal demise	2 (2%)

*Outcome variables not mutually exclusive (e.g., one angular pregnancy could result in both live birth and hysterectomy).

Table 2: Angular pregnancy outcomes by time period (total N=85).

Outcome	Time period 1 (1934-1981) N=61	Time period 2 (1981-2013) N=24	P value*
Live birth	15/61=25%	6/24=25%	0
Maternal death	4/61=7%	0/24=0%	0.1988
Uterine rupture	17/60=28%	7/24=29%	0.9048
Abortion-spontaneous	15/60=25%	0/24=0%	0.0074*
Abortion-therapeutic	13/61=21%	10/24=42%	0.0844
Hysterectomy	15/61=25%	7/24=29.2%	0.6645

*Indicates statistical significance.

the other unknown but "near term" [12,47]. Additionally, there were five cases of placenta accreta/increta/percreta (5/85=6%), three cases of retained placenta / incomplete removal of placenta (3/85=4%) and one case of placental abruption reported.

Subset analysis

Additional subset analyses were performed on 26 cases (26/85=31%) of angular pregnancy which were not intervened upon, either because they were managed expectantly (10) or were diagnosed close to viabilityas an unexpected finding (16). Overall, of these 26 angular pregnancies, there were 18 live births, corresponding with a live birth rate of 69% (18/26); six spontaneous abortions (6/26=23%); two hysterectomies; one case of placenta accreta; one therapeutic abortion (elective suction curettage at 14 weeks when thinned myometrium demonstrated on MRI [48]; and one uterine rupture (at 21weeks yielding a still born 450g infant) [18]. If the 10 cases of angular pregnancy diagnosed in the early pre-natal period (≤12 weeks) and managed expectantly until the second or third trimester are examined alone, then the live birth rate was 80% (8/10) (the other two are the therapeutic abortion and uterine rupture case detailed above). Alternatively, if the cases of therapeutic (1) and elective abortion (6) are excluded (26-7=19) in order to examine the natural course / outcome of angular pregnancy in yet another way, then of the 19 remaining cases all but 1 resulted in a live birth (18/19=95%).

Further subgroup analysis was performed on pregnancy outcome according to time frame, with cases from 1934-1981 in time period one (N=61) and cases from 1982-2013 in period two (N=24). The results are summarized in Table 2, with highlights here. The live birth rate was equivalent in time period one (15/61=25%) and time period two (6/24=25%).Although the difference in the rate of therapeutic abortion trended towards significance (p=0.0844) -- being higher in time period two (10/24=42%) than in time period one (13/61=21%) -- the only statistically significant difference between time periods one and two was with the spontaneous abortion rate, which was higher in time period one (15/60=25%) than in time period two (0/24=0%) (p=0.0074). In sum, there was no statistically significant difference between time periods one and two with respect to the rates of maternal death, uterine rupture, or hysterectomy.

Discussion

In summary, the objective of this study was to perform a review of reported angular pregnancies cases to determine outcomes, and the principal findings were that the live birth rate was 25% or even higher (69%) if the angular pregnancy was expectantly managed. While no maternal deaths have been reported in roughly the last five decades, the condition has been associated not only with an 18% overall spontaneous abortion rate, but also with the serious complication of uterine rupture (28-29%).

In this analysis, the uterine rupture rate was 28-29%, higher than previously reported. Specifically, in 1981, Jansen and Elliot reported 13.6% as a "crude estimate of the chance of an angular pregnancy causing an otherwise normal uterus to rupture" [59]; all of the cases in our series involved "normal uteri," with no Mullerian duct anomalies noted. Possible reasons for this difference include different sample sizes (N=39 versus N=39+46=85) and, although our data also has the limitation of selection bias, the advent of the worldwide web may potentially have minimized barriers to reporting. To contextualize

these numbers, the rate of uterine rupture in women attempting a vaginal birth after cesarean (VBAC) is 0.5-1% [6], and VBAC in the clinical setting, in one study, accounted for 92% of all uterine ruptures [63]. Possible pathophysiological mechanism which could be responsible for uterine rupture in angular pregnancy, according to Jansen and Elliot, is that the uterus is "understandably susceptible to rupture if the gestational sac grows in the weakened uterine angle" [59]. Although our rates of maternal death (5%) and hysterectomy (26%) may initially seem high as well, they are similar to the rates calculated from the numbers reported by Jansen and Elliot in 1981 (1/39=3% maternal death rate; 7/39=18% hysterectomy rate) [59]. Likewise, our 6% rate of placenta accreta/increta/percreta is similar to the rate calculated from the numbers reported by Jansen and Elliot in 1981 as well (4/39=10%).Of note, recently, it has become possible to treat placenta accreta conservatively [64].

The spontaneous abortion rate associated with angular pregnancy in this study was 18% overall, lower than previously reported. In 1981, Jansen and Elliot reported a spontaneous abortion rate of 38.5% [5]. Possible reasons for this difference include differences in sample size, but also different time periods. In other words, prior to 1981, in a less litigious world, more angular pregnancies may have spontaneously aborted because they were not intervened upon as frequently; the fact that no spontaneous abortions were reported in time period two may be partly explained by higher rates of elective termination -- the fact that no maternal deaths were reported in time period two may also be partially explained by the same reason. Furthermore, without the diagnostic sophistication available in more recent decades, diagnosis of angular pregnancy was often not made until after a spontaneous abortion occurred.

The live birth rate in time period one (1934-1981) and time period two (1982-2013) were the same (25%), which is interesting given that the first period spans a large amount of time in which medical care dramatically changed. This may be a major reason for little difference in outcomes: in other words, if the time period one had been prior to 1950 or 1960, and then time period two from 1950 or 1960 to modern day, then the analysis of the difference in outcomes by time periods may have been very different. However, our rationale for chosen division in time (1934-1981, 1982-2013) was that 1981 was the last year a major review and meta-analysis on the subject was published [59]. On the other hand, this consistency over time -- despite marked differences in terms of medical knowledge, diagnostic technology, and management options over the 80 years encompassed in this study – could arguably support the reproducibility and reliability of this 25% figure irrespective of other variables. Furthermore, this 25% LBR is consistent with Jansen and Elliot's 1981 article of 39 cases, which has a calculated LBR of 28% (11/39) [59].

In this subset, on the other hand, the live birth rate was 69% or higher, consistent with previous researchers [9, 15, 16, 19] who have pointed out that the live birth rate of angular pregnancy is probably higher than reported due to the fact that cases of angular pregnancy tend to be diagnosed only after severe complications (i.e., those that are asymptomatic may go undiagnosed), which skews the numbers by creating an artificially high proportion of bad outcomes and leaves the rate of uncomplicated angular pregnancy ambiguous.

Selection and reporting bias have already been mentioned, and additionally, there is reasonable concern about publication bias since it is more likely that positive results (those that ended in live born) may be published. Also, despite our strict operational definitions, there is a possibility that some 'angular pregnancies' included in this analysis were misdiagnosed interstitial pregnancies when they originally occurred. In other words, cases of interstitial pregnancy may have been confused as angular (or vice versa) due to the difficulty in distinguishing these two types of pregnancy, especially the cases reported in the first period of the study when ultrasound was more primitive – since the differences on imaging are subtle, it is important to note this is as a salient limitation; and although a complete discussion of the features and differences of these conditions are beyond the scope of this manuscript, this has been addressed by

senior author of this paper in a recent review article [65], as well as elegantly by Tanaka et al. [66] in a case series with imaging differences demonstrated on both 2D- and 3D-ultrasound. Another study limitation was that, as with meta-analyses, there was some variability in the associated findings of the individual cases in our cohort – for example, some had associated myomas (4/85=4.7%) [21,26,28,52] and others associated mullerian duct anomalies (bircornuate x 2, septate, and subseptate, respectively, thus also (4/85=4.7%) [5,35,36,51] – and thus a degree of heterogeneity. Additionally, a benefit but also a drawback of this study is the number of years it covers (1934-present), during which time there has been significant variation in medical diagnostics and management; we tried to address this by creating time period subgroups, however, even in the past 30 years there have been significant changes in medicine and thus pooling results may have introduced bias [67].

In conclusion, the objective of this study was to perform an analysis of reported angular pregnancy cases in order to determine outcomes, and the principal findings were that although live birth is possible (25-69% of the time), the high rate of uterine rupture (28-29%) makes these pregnancies particularly high risk. The clinical implications of these findings are that, given the seriousness of this complication, additional research should focus on updating the angular pregnancy criteria from 1981. With special attention to defining the key imaging findings, this would help optimize the chance of making an accurate and timely diagnosis and offer better informed decision-making regarding management.

While this study nevertheless represents the largest aggregation of angular pregnancy cases to date, given data limitations, perhaps the only reasonable conclusion is that more research is needed regarding this highly controversial diagnosis. Specifically, the prevalence and clinical significance of 'angular pregnancy' could only be properly determined by conducting a large prospective multicenter study with clearly defined diagnostic criteria – updated since 1981with special attention to how to differentiate angular from interstitial pregnancies on imaging -- and robust follow up.

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