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REVIEW

Secondary Infertility due to Fetal Bone Retention

A systematic literature review

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abstract: Prolonged intrauterine retention of fetal bones during an abortion procedure can lead to secondary infertility. This review aimed to raise awareness among obstetric/gynaecologists about the possibility of this condition. A total of 17 case reports, seven case series and one retrospective study were included in this review, with 75 patients in total. Overall, 60% had a pregnancy termination in the second trimester, while 20% had a termination during the first trimester. Hysteroscopic resection was used to remove the intrauterine fetal bones in 69% of patients. In total, 59% of patients conceived following the procedure, 1% conceived despite the presence of intrauterine bones, 24% could not conceive at the time of the study and 16% had an unknown outcome. Transvaginal ultrasound was used for diagnosis in 41 (55%) patients, while pelvic ultrasound was used in 21 (28%) patients. In conclusion, secondary infertility is a common occurrence after a dilation and curettage procedure partially due to fetal bone retention. The gold standard for an accurate diagnosis and treatment is hysteroscopy.

Keywords: Incomplete Abortion; Abortion; Therapeutic Abortion; Miscarriage; Infertility.

According to the United Nations medium-variant projection, the global fertility rate declined from 3.2 live births per woman in 1990 to 2.5 in 2019 and is expected to reach 2.2 live births per woman in 2050 and 1.9 in 2100.[1] Each year, more than 227 million women become pregnant worldwide, out of which roughly two-thirds deliver live infants, while the remaining one-third end in miscarriage, stillbirth or induced abortion.[2] Globally, one in four pregnancies (25%) end in abortion, of which nearly half (45%) are unsafe abortions.[3] Worldwide, 8–12% of couples of reproductive age are affected by infertility.[4] It is estimated that one in four couples in developing countries and one in seven couples in developed countries suffer from infertility. The prevalence of infertility in some parts of the world, such as South and Central Asia, the Middle East, North Africa, Sub-Saharan Africa and Central and Eastern Europe, is as high as 30%.[5] In the USA, about 1.3 million women are treated annually for infertility, while 2% undergo treatment with assisted reproductive technology.[6]

Secondary infertility is the most common form of infertility. It is commonly seen in areas with unsafe abortion practices and maternity care, which are often associated with increased chances of infection.[7] Post-abortion infection can lead to future fertility problems resulting from damage to the fallopian tubes or direct damage to the endometrial lining leading to adhesions (Asherman's syndrome). Rarely, surgical mid-trimester abortions can lead to retained fetal bones and cause subfertility.[8] As reported by Izhar *et al.*, prolonged intrauterine retention of any fetal bone can lead to secondary infertility.[9] Although rare, retained fetal bones are more commonly seen in an anomalous uterus.[10] The exact incidence remains unclear; however, the incidence was reported to be 0.15% among 2000 diagnostic hysteroscopies.[9,11] Apart from subfertility, retained fetal bones may also present with chronic pelvic pain, dysmenorrhoea, abnormal uterine bleeding and dyspareunia.[10] Prolonged retention of fetal bones may lead to chronic inflammation and endometrial damage, making it harder to achieve fertility.[10]

The present review was focused on outlining the pathophysiology, clinical presentations, diagnostic modalities and treatment options and outcomes in patients with secondary infertility due to fetal bone retention. Sometimes, patients with this condition are asymptomatic and fetal bones can be found as an incidental finding on an ultrasound or hysteroscopy, as part of the infertility workup.[10] A high level of suspicion is necessary to diagnose this rare condition; hence, this review aimed to raise awareness among obstetric/gynaecologists about the possibility of this condition.

Pathophysiology and Hypothesis of Secondary Infertility due to Fetal Bone Retention

Prolonged intrauterine retention of any fetal bone can lead to secondary infertility. The earliest report of calcified tissue of fetal origin *in utero* goes back to 1966.[12] These calcified tissues, when deeply embedded in the uterine mucosa, may present with the same contraceptive effect as an intrauterine contraceptive device, thereby causing secondary infertility.[13,14] On imaging, these tissues usually present as echogenic

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foci partially embedded in the endometrial lining, an intrauterine foreign body, thin plates of bone or many fetal bones with a nearly intact morphology.[9,12,15,16] Microscopic examinations have revealed necrotic bony trabeculae, bone marrow and chronic inflammation in the intervening spaces within the endometrium during its proliferative phase.[16,17]

In 1982, Dawood *et al.* posited that the presence of the fetal bones can act as uterine synechiae or an intrauterine device (IUD) and thus could prevent pregnancy. According to their study, fetal bones near the fundal region also elevated the concentration of endometrial prostaglandin F2 alpha in that region, leading to infertility.[18] In addition, Lewis *et al.* discovered that the pattern of prostanoid increase was similar to that seen in IUD users.[19] Another pathogenesis for this condition is endometrial osseous metaplasia, a rare entity.[20] However, a previous pregnancy history is reported in >80% of these cases.[21] There are two theories regarding the origin of osseous metaplasia: 1) persistence of embryonic bones that keep developing after curettage; and 2) induction of a process of osteogenesis by one's embryonal cells, provoking the osseous differentiation of hypothetical pluripotent endometrial cells. This process can be differentiated from retained fetal bones by comparing the patient's short tandem repeats and the bony sample.[22]

In a study by Wani *et al.*, histopathological examination of retrieved endometrial tissue from 10 patients revealed nonspecific lymphocytic infiltrate with interspersed lamellar bone in six (42.8%) patients and trabecular bone in four (28.5%) patients with scanty endometrial glands and stroma in various hormonal phases. These results confirmed the diagnosis of osseous metaplasia of the endometrial lining.[23]

Methods

PROTOCOL

This systematic review consists of analysis from published case reports, case series and retrospective studies. It was conducted according to the standards and guidelines established in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

SEARCH STRATEGY

A systematic literature search of four academic databases was conducted in October 2021: PubMed (National Library of Medicine, Maryland, USA), ScienceDirect (Elsevier, Amsterdam, Netherlands), Cochrane (Cochrane Library, London, England) and Google Scholar (Google, California, USA). The search included all relevant articles from inception up to October 2021. Regular terms used were 'infertility' and 'retained fetal bones'. Terms used from the Medical Subject Headings database were 'infertility, female' and/or 'retained' and/or 'fetal bones' and/or 'abortion'. The search terms were kept broad to encompass all possible relevant studies. Inclusion and exclusion criteria were then applied. The first and second authors screened the title and abstract, then the full paper was read to determine its relevance. At the end of the search, any duplicate articles were eliminated using Microsoft Excel. All selected articles reporting patients with retained fetal bones from a previous pregnancy termination who presented with infertility were included in the analysis.

STUDY SELECTION, EXTRACTION AND ANALYSIS

The literature search yielded 1,119 studies. Study selection was completed by three independent, parallel reviewers and performed in two separate stages: (1) title/abstract screening, followed by (2) full-text screening. Data extraction was performed by three investigators, who resolved discrepancies via consensus. A total of 410 duplicates were manually removed and the three investigators independently reviewed all titles and abstracts. Subsequently, 600 studies were deemed irrelevant and excluded after screening their titles and abstracts. The full texts of the articles regarded as potentially eligible for consideration were extracted and screened for further analysis based on the predefined inclusion and exclusion criteria. Finally, 25 studies were selected for inclusion in the review after the full-text screening [Figure 1]. Disagreements between the authors were resolved through consensus and active discussion.

INCLUSION/EXCLUSION CRITERIA

The eligibility criteria were determined following the patient, intervention, comparison and outcome approach. The following inclusion criteria were considered: participants of all ages, articles published in and after 1982, human subjects and articles written in English. The exclusion criteria consisted of review articles, animal studies, studies published in a language other than English and the absence or unclear reporting of the infertility complication status in post-abortion patients.

QUALITY APPRAISAL

The first and second authors performed quality appraisals. A total of 17 case reports, seven case series and one retrospective study were included in the review, comprising a total of 75 patients.

Results

CLINICAL MANIFESTATIONS

Overall, 25 published papers with a total of 75 cases of retained fetal bones were included. In all 75 cases, women presented with infertility after the termination of pregnancy in either the first or second trimester. Other presenting symptoms included dysmenorrhoea, menorrhagia, chronic pelvic pain, dyspareunia and vaginal discharge. The comprehensive literature review concluded that most patients had a previous pregnancy termination during the second trimester. A total of 45 (60%) cases had a termination in the second trimester, while 15 (20%) had a pregnancy termination during the first trimester. The exact date of termination was unknown for 15 (20%) patients. The interval between termination and reporting of symptoms varied. The shortest interval recorded was 12 months and the longest was 180 months.[24,25] In a study by Petrakis *et al*., a patient presented with chronic pelvic pain and infertility 12 months after a miscarriage at 19 weeks gestation due to placental abruption.[24] A summary of cases with retained fetal bones seen in patients presenting with infertility after either a spontaneous or induced pregnancy termination is provided in Table 1.[8–10,13,14,16,18,24–41]

DIAGNOSIS

Pelvic ultrasound proved to be an excellent imaging tool for diagnosis in any female with infertility; transvaginal and abdominal ultrasound was used in 41 (55%) and 21 (28%) of the 75 patients, respectively. Areas of interest during the transvaginal ultrasound (TVS) included the patency of fallopian tubes, the size of the uterus and the presence of echogenic areas suggestive of fetal bones in the endometrial cavity. One (1%) patient had a saline infusion sonography (SIS) procedure performed in addition to a TVS, in which highly echogenic areas in the anterior wall of the uterus were visualised.[9] Hysterosalpingogram (HSG) was another method used in seven (9%) patients, which looks for filling defects and space-occupying irregularities in the uterine cavity and fallopian tubes. Additionally, hysteroscopy provided both diagnostic and therapeutic benefits in five (7%) patients.

TREATMENT AND OUTCOME

A hysteroscopic resection alone was performed in 52 patients (69%), while it was performed along with dilation and curettage (D&C) in two (3%) patients. Petrakis *et al*. presented a case where one (1%) patient had a hysteroscopy scheduled but did not comply with treatment recommendations.[25] Other treatment methods used included D&C without hysteroscopy in 17 (23%) patients and dilation and evacuation (D&E) in three (4%) patients. Hysteroscopic resection was used most frequently for the removal of intrauterine fetal bones [Table 1].

Regarding patients experiencing a successful pregnancy post-treatment, the review revealed that 44 (59%) patients conceived following the removal of retained intrauterine fetal bones. One (1%) case was identified in which a patient conceived despite the presence of intrauterine bone fragments.[24] In comparison, 18 (24%) patients had not conceived at the time of the study. The remaining 12 (16%) patients either were not followed up for infertility or had other outcomes, or the details of their follow-up are unknown. Other outcomes following treatment that were reported included the patient's return to a normal menstrual cycle and the resolution of presenting symptoms.

Discussion

Although rare, the intrauterine retention of fetal bones is a potential complication following an abortion, often in the second or third trimester.[34] Abortions occurring in the first trimester, when fetal bone ossification has not yet completely occurred, could involve dystrophic calcification of retained products that could also lead to intrauterine bone formation.[10] However, it could also occur secondary to osseous

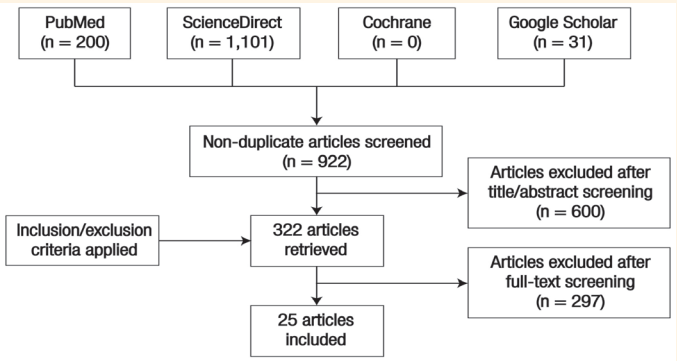

Figure 1: PRISMA flow diagram depicting search strategy of all relevant articles from inception up to October 2021.

Table 1: Summary of cases of retained fetal bones seen in patients presenting with infertility after either a spontaneous or induced pregnancy termination[8–10,13,14,16,18,24–41]

Authors and year of publication	Number of cases presenting with infertility	Age in years	Interval between TOP or miscarriage and diagnosis in months	Gestational age at TOP or miscarriage in weeks	Clinical presentation	Diagnostic imaging method	Treatment	Outcome
Srofenyoh *et al.*[8] (2006)	3	35 30 42	NK	16 (n = 2); NK (n = 1)	Chronic pelvic pain (n = 1); Dyspareunia (n = 1); Secondary Infertility (n = 1)	Pelvic ultrasound	D&E	Conceive (n = 2); Had not conceived (n = 1)
Izhar *et al.*[9] (2015)	1	36	NK	20	Secondary infertility	Transvaginal ultrasound and SIS	D&C	Scheduled for repeat SIS and kept on high-dose oestrogen. Has not conceived
Gainder *et al.*[10] (2018)	18	NK	>24 (n = 5); 24–36 (n = 6); >36 (n = 7)	First Trimester (n = 5); Second Trimester (n = 13)	Secondary infertility; Menorrhagia (n = 5); Amenorrhoea (n = 2); Metrorrhagia (n = 4); Chronic pelvic pain (n = 2)	Pelvic ultrasound (n = 17); Hysteroscopy (n = 1)	Hysteroscopy (n = 15); D&C (n = 3)	Conceived (n = 5); Had not conceived (n = 7); Not followed up for conception (n = 6)
Lanzarone and Pardey[14] (2009)	1	36	NK	NK	Secondary infertility	Hysteroscopy	Hysteroscopy	SIS determined a normal cavity
Patil *et al.*[13] (2013)	1	28	NK	6	Menorrhagia	Hysteroscopy	Hysteroscopy	NK
Dajani and Khalaf[16] (1985)	1	26	18	18	Secondary infertility	Hysterosalpingogram	D&C	Conceived
Dawood and Jarrett[18] (1982)	1	22	72	10	Secondary infertility	Hysterosalpingogram	Hysteroscopy with D&C	Had not conceived.
Petrakis *et al.*[24] (2019)	1	28	12	19	Chronic pelvic pain	Transvaginal ultrasound	Hysteroscopy scheduled but did not comply.	Conceived without removal of fetal bones.
Moon *et al.*[25] (1997)	11	26–37	12–60 (n = 10); 180 (n = 1)	16–24	Secondary infertility	Transvaginal ultrasound	D&C	Conceived (n = 10); Bilateral tubal obstruction. Had not conceived (n = 1)
Melius *et al.*[26] (1991)	1	33	108	NK	Secondary infertility	Hysterosalpingogram	Hysteroscopy	Had not conceived.
Chan[27] (1996)	1	34	108	16	Secondary infertility, Dysmenorrhoea	Transvaginal ultrasound	Hysteroscopy	Returned to a normal menstrual cycle. Not followed up for conception.
Arora *et al.*[28] (1998)	2	28 27	Case 1: 48 Case 2: NK	Case 1: 16 Case 2: 12	Secondary infertility	Hysterosalpingogram	Hysteroscopy	Case 1: Returned to a normal menstrual cycle Case 2: Conceived
Tulandi and Sammour[29] (2001)	1	33	96	6	Secondary infertility	Hysterosalpingogram	Hysteroscopy	NK
Elford and Claman[30] (2003)	1	36	15	Late first trimester	Secondary infertility	Pelvic ultrasound	Hysteroscopy with D&C	Conceived
Goldberg and Roberts[31] (2008)	1	32	NK	22	Secondary infertility	Transvaginal ultrasound	Hysteroscopy	Conceived

TOP = termination of pregnancy; NK = not known; D&E = dilation and evacuation; SIS = saline infusion sonography; D&C = dilation and curettage.

Table 1 (cont'd.): Summary of cases of retained fetal bones seen in patients presenting with infertility after either a spontaneous or induced pregnancy termination[8–10,13,14,16,18,24–41]

Authors and year of publication	Number of cases presenting with infertility	Age in years	Interval between TOP or miscarriage and diagnosis in months	Gestational age at TOP or miscarriage in weeks	Clinical presentation	Diagnostic imaging method	Treatment	Outcome
Kramer and Rhemrev[32] (2008)	1	32	96	12	Secondary infertility	Hysteroscopy	Hysteroscopy	Conceived
Singla *et al.*[33] (2012)	1	23	36	10	Secondary infertility	Transvaginal US	Hysteroscopy	Advised a hysterosalpingogram for tubal patency. Had not conceived.
Xiao *et al.*[34] (2014)	1	30	108	15	Secondary infertility	Hysteroscopy	Hysteroscopy	Conceived
Mishra *et al.*[35] (2018)	1	28	60	15	Secondary infertility	Transvaginal ultrasound	Hysteroscopy	Conceived
Mahdavi *et al.*[36] (2019)	1	25	24	15	Secondary infertility	Hysterosalpingogram	Hysteroscopy	Conceived
Graham *et al.*[37] (2000)	11	23–36	24–144	10 (n = 2), 12 (n = 1), 14 (n = 3), 16 (n = 2), 20 (n = 1), 24 (n = 1), 26 (n = 1)	Secondary infertility	Transvaginal ultrasound	Hysteroscopy	Conceived (n = 8); Had not conceived (n = 2); NK (n = 1)
Pereira *et al.*[38] (2014)	7	24–40	NK	NK	Secondary infertility	Transvaginal ultrasound (n = 5); Hysteroscopy (n = 2)	Hysteroscopy	Conceived (n = 5); Did not conceive (n = 2)
Grigore *et al.*[39] (2014)	2	41	NK	NK	Secondary infertility	Transvaginal ultrasound	Hysteroscopy	Case 1: Conceived;
		34						Case 2: Resolution of symptoms
Bozdag *et al.*[40] (2015)	1	30	10	NK	Secondary infertility	Transvaginal ultrasound	Hysteroscopy	Conceived
Awowole *et al.*[41] (2021)	4	NK	NK	NK	Secondary infertility	Transvaginal ultrasound	Hysteroscopy	Conceived

TOP = termination of pregnancy; NK = not known; D&E = dilation and evacuation; SIS = saline infusion sonography; D&C = dilation and curettage.

metaplasia due to the chronic inflammation of the endometrium.[34] Hypercalcaemia, hyperphosphatemia and hypervitaminosis D are rarer causes of this endometrial calcification.[10] The incidence of this complication is thought to be underestimated, as symptoms experienced by patients are not readily attributed to the abortion, leading to a considerable delay between the abortion and diagnosis.[42]

Retained fetal bones exert an intrauterine device (IUD)-like effect, resulting in secondary infertility, and their removal could reverse this effect.[34] As seen from the outcomes of included case reports, D&C procedures for the evacuation of the prior non-viable fetus had preceded secondary infertility and the removal of retained fetal bones, most commonly via hysteroscopy, allowed these patients to conceive.[6,16,24,25,30–36]

The present review found that hysteroscopic removal was performed in 69% of patients, enabling 59% to conceive after the procedure. Other treatment methods used included D&C without hysteroscopy in 23% of patients and D&E in 4% of patients.

In a study by Gainder *et al.*, the data of 6,435 patients who visited a fertility clinic in India were retrospectively reviewed, out of which 18 patients received 'retained fetal bone' as the sole diagnosis for their infertility.[10] All patients underwent diagnostic hysteroscopy and had the bony fragments removed via hysteroscopy (n = 15) or D&C (n = 3). Despite following up on 12 of the 18 patients for up to 6 years, spontaneous conception was only noted in five patients. It must be noted that these five patients had presented for secondary infertility within 3 years of their previous abortion, while the remaining seven had presented after >3 years. This finding led the authors to conclude that any changes associated with the retention of bony fragments are expected to regress with a return of fertility only if the bony fragments are removed quickly and provided there

is no tubal damage or formation of uterine synechiae following the abortion. The long-term presence of bony fragments in the endometrial cavity could have led to endometritis, thus accounting for persistent infertility. The authors also postulated that a few bony fragments could have become so deeply embedded in the endometrium that they could not be successfully removed; thus, these could have continued to act as foreign bodies, preventing intrauterine pregnancy.[10]

Petrakis *et al*. similarly reported that achieving childbearing is possible, with spontaneous conception and a high live birth rate, once bony fragments have been removed from the uterine cavity. However, Petrakis *et al*. also reported the case of a successful live pregnancy, conceived spontaneously and carried to term, in a patient with calcium salt deposits in the placenta and the intrauterine retention of fetal bones from a previous miscarriage at 19 weeks gestation a year prior.[24] To date, this is the only reported case where a patient could conceive despite the presence of intrauterine fetal bones.

In addition to secondary infertility, intrauterine fetal bones could also cause abnormal uterine bleeding, menorrhagia, dysmenorrhea, chronic pelvic pain and abnormal vaginal discharge.[34] It was suggested that pelvic pain and dysmenorrhoea could be due to an increase in the levels of prostaglandins from the inflammatory reaction.[10] Removal of bony fragments could thus reverse these symptoms.[8,10,15,27]

Pelvic ultrasounds, pelvic X-rays, hysterosalpingograms and hysteroscopies have been used to detect intrauterine bony fragments.[10,37] Shadows observed on ultrasonography are often not definitive for diagnosis but could guide the hysteroscopic removal of these bony fragments.[10] A report of calcifications in the endometrium by radiologists is also not definitive for diagnosis. However, it should still raise suspicion about retained fetal bones, especially when coupled with a history of prior abortion.[11] An accurate diagnosis is best obtained via hysteroscopy, which will reveal osseous fragments embedded within the endometrium. Although D&C may also be employed to remove these bony fragments, it is a less commonly choice for treatment. Hysteroscopy plays a vital role as a management option, as bony fragments may simultaneously be retrieved during the procedure.[10]

Conclusion

Secondary infertility is a common occurrence after a D&C procedure. In second-trimester abortions, fetal bone retention could be one of the causes of secondary infertility. The theories discussed in the studies of infertility due to fetal bone retention included elevated endometrial prostaglandin F2, osseous metaplasia and chronic inflammation. To achieve another pregnancy, removal of these retained bones is recommended. The sooner the removal is made, the better are the chances of achieving a future pregnancy. Very rarely has there been reported conception despite the fetal bones retained in the uterine cavity. Besides secondary infertility, patients can also present with dysmenorrhea, menorrhagia, chronic pelvic pain, dyspareunia and vaginal discharge. The gold standard for an accurate diagnosis is hysteroscopy, which provides the added benefit of removing these fragments at the same sitting. Therefore, to improve outcomes and restore fertility in women presenting with secondary infertility after having a prior abortion, physicians must be wary of the possibility of fetal bone retention.

AUTHORS' CONTRIBUTIONS

AA conceptualised and designed the work. AA and JAL collected, analysed and interpreted the data. AA, UM, HL and CP drafted the manuscript. All authors critically revised the manuscript and approved the final version.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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